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Finally, following the implications in the last two paragraphs, one may, often to great advantage, introduce in the treatment of cardiovascular disease occasional "rest days" or even weeks in which the word "rest" means *rest from medicines*. Morale, appetite, well-being, and even the spark of life itself may be revived by such a procedure.

#### ACUTE RHEUMATIC HEART DISEASE WITHOUT MYOCARDIAL FAILURE

Case I.—A. B., a schoolboy six years of age, was always well previously; his tonsils had been removed at the age of four because they were considerably enlarged. He has been ill now for two months with malaise, occasional oral temperatures up to 100.5° F., muscle and joint pains without swelling or tenderness, and mild involuntary twitching of both arms and face. He is pale, has lost appetite and weight, and is restless and irritable. He has been out of school and in bed off and on during this period of time. There has been no dyspnea, palpitation, or chest pain.

On examination the patient is seen to be a delicate little boy with occasional twitching of the right arm and face. Physical examination otherwise shows no abnormality except for slight enlargement of the heart, with a moderately loud systolic murmur at the apex and a very short mid-diastolic murmur in the same area. Blood examination shows a white count of 12,000 with polymorphonuclears increased, hemoglobin 60 per cent, and red count 4,000,000. The sedimentation rate is increased moderately. The urine is normal. x-Ray examination shows the heart to be slightly enlarged, with slight prominence of the pulmonary artery and its branches. The electrocardiogram shows normal rhythm with a P-R interval of 0.2 of a second, which is slightly but distinctly increased beyond the normal for this age.

The *diagnosis* is obviously that of active rheumatism of childhood involving the heart. The murmurs are undoubtedly the result of slight dilatation of the heart and are not due to valvular deformity, which in the course of these two months has not had time to develop.

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ease on the myocardium with the tendency to cardiac dilatation which may easily increase and tend to become permanent if there is extra strain on the heart during this period of active involvement.

To support the morale and to foster happiness for the child during this long period of bed rest, various measures have been introduced, one of the most practical of which has been that of the *In-Bed Club* worked out by Miss Terry and her associates in the Children's Clinic at the Massachusetts General Hospital. Included under such a plan are the In-Bed badge, In-Bed jacket, In-Bed magazine, and recreational and occupational therapy as soon as the child is improved enough or is in condition, even from the outset, to have mild entertainment of this nature in bed. (For details, the reader is referred to the article by Miss Edith Terry in the *New England Journal of Medicine*, 224:632, 1941.)

Equally important with rest in bed is the *strict avoidance of fresh respiratory infections* brought in by members of the family, friends, doctors, or nurses. It is unfortunately true that even in the best hospital reactivation of a subsiding rheumatic infection not rarely results from the introduction of a respiratory infection from the outside which tends to spread like wild-fire through the institution. One of the reasons for sending rheumatic children to Florida in the past has been to protect them from the more virulent hemolytic streptococcus colds which are less likely to exist in the tropics and semitropics than in the North in the winter and spring months. However, the problem can be faced in the North and even in cold outdoor weather, as demonstrated by Dr. John Hubbard during the past few winters at a former tuberculosis sanatorium at Sharon, Massachusetts, where rheumatic children, though outdoors, have improved steadily by careful avoidance of the introduction of respiratory infections, largely by limitation, both in number and in duration, of the visits of relatives and friends and the fact that such visits take place in the open air, there thus being no enclosed space to concentrate any bacteria (*New England J. M.*, 223:968, 1940).

Other aspects of treatment are relatively unimportant. The *diet* should be a nutritious mixed diet of approximately 1600 to 1800 calories. When convalescence begins after the acute

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**Treatment.**—This is to be carried out as before but by more absolute *bed rest*. Sometimes the head and chest must be elevated to whatever position is most comfortable for the child. Analgesics in the form of *salicylates*, especially aspirin (acetyl-salicylic acid) 10 grains every three to four hours, helps to get rid of the joint pain and may perhaps aid in the subsidence of the pericarditis. If the distress is considerable, small doses of *codeine sulfate* or *morphine sulfate*,  $\frac{1}{4}$  grain of the former or  $\frac{1}{8}$  grain of the latter subcutaneously every few hours, may be needed for pain or distress. Ordinarily *digitalis* is the drug of choice for congestive heart failure but it has been found in the case of rheumatic myocarditis with cardiac dilatation that *digitalis* is relatively ineffective or even unwise. *Theodate* (theobromine sodium acetate) in the dosage of 15 grains three times a day has proved a helpful diuretic in these children (Walsh and Sprague, J.A.M.A., 116:560, 1941).

Gradually, if the child survives, there is a subsidence of the evidences of the congestive failure and a return very slowly to a fairly normal state of health, but almost invariably with some persisting cardiac enlargement to which may be added in the course of time deformity of the heart valves. Long-continued bed rest for months and the use of iron and vitamins, and of sunlight and care to avoid infection should be the program until return to full health.

### SUBACUTE BACTERIAL ENDOCARDITIS

**Case III.**—E. F., a young woman aged twenty-one years, had been known for ten years to have valvular disease following rheumatic fever at the age of eleven. After excellent health during this decade, she began two months ago to feel tired and listless. Gradually, her malaise increased until finally, a few days ago, she sought medical advice. She thought she had had a little fever off and on. There had, however, been no pain, dyspnea, palpitation, syncope, or cough.

Physical examination reveals a slightly underweight young woman, rather pale, with a mouth temperature of 101° F. The only other abnormal findings

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There is one other drug that has been reported as helpful or even curative in a few cases. This is *neoarsphenamine*, which has been recommended by Osgood of Portland, Oregon, to be given in the following manner (personal communication):

"The unit dose in milligrams of neoarsphenamine is determined by multiplying the body weight of the patient in pounds by 0.8 mg. In subacute bacterial endocarditis and serious chronic staphylococcic infections, one unit dose from a fresh 0.15 gram ampoule is given intravenously every four hours for four doses the first day and every eight hours (three doses per day) for the following five days. If the temperature during this initial six-day period has been lowered to normal or nearly to normal, one should alternate three to six day rest periods with three-day courses of therapy. The dosage on the first day of each new course of therapy is similar to the first day regimen, namely, one unit dose every four hours for four doses. The dosage on the second and third days of each new course of therapy is similar to the regimen of the second day, namely, one unit dose at eight-hour intervals. These alternate courses of therapy and rest periods are continued for about sixty days, unless evidence of serious toxicity develops. The rest periods are gradually prolonged until during the second month of therapy they are of six days' duration.

"If, during the initial six-day period, the temperature is somewhat lowered \* Our experience in the past year has strongly suggested that heparin may be a valuable adjunct—there is little or no real danger in its use. Five out of six recovered cases of ours (Leach, Faulkner, Duncan, McGinn, Porter, Kelson, and White, 1940-1941) received heparin as well as sulfapyridine. We have been disappointed in the effect of heat therapy to date.

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able for a long life; in fact, the expectation without treatment would be only a few years at best. However, treatment can change this prospect, sometimes to a considerable degree.

**Treatment.**—Here specific therapy comes into play in one of the few instances in heart disease when such therapy is successful, but even here specific therapy alone is not enough. It is just as important for the victim of this serious disease *to avoid physical strain* as it is to take arsenic or bismuth or mercury. The first essential, then, is to have this man quit completely all physical labor during the first few months of treatment. If that is not possible, then the work should be changed to as light a job as possible. Undoubtedly, the work of heavy laborers is one of the most important causes of progression of aortic strain, dilatation and death, even when adequate chemotherapy is in progress. The plan of specific drug treatment is as follows:

It is preferable to begin with *bismuth*, in the form of the insoluble salt by intramuscular injection, in the dosage of 0.1 gm. ( $1\frac{1}{2}$  grains) every four days for four weeks, and then 0.2 gm. (3 grains) weekly for another eight weeks. There should then follow, if the patient's condition is favorable, a course of arsenical injections, either *mapharsen*, beginning with 0.01 gm. intravenously and increasing slowly to a maximum of 0.04 gm., or *neoarsphenamine*, beginning with 0.1 gm. intravenously and increasing slowly to a maximum of 0.4 gm., weekly injections to be made over a period of twelve weeks. Simultaneously with the bismuth and arsenic, *potassium iodide* may be given by mouth, starting with the dose of 1.0 gm. (15 grains) three times daily and slowly increasing to 3.0 gm. (45 grains) three times daily. The drugs must be decreased in dosage or stopped if toxic symptoms arise; such toxic symptoms consist chiefly of salivation and nausea in the case of bismuth, of immediate collapse (nitritoid reaction) or erythema and liver damage with jaundice in the case of neoarsphenamine, and urticaria, erythema, lacrimation and coryza in the case of potassium iodide.

This treatment should be continued for years with an annual checkup of the serologic reaction, but whether the Wassermann becomes negative or not, therapy should not lapse. The courses of arsenic and bismuth should alternate without pause

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**Treatment.**—In the first place it is of vital importance for the doctor, and the patient too, to understand what is going on. An unhurried, frank and detailed discussion with the patient about what is wrong is infinitely worth while, at the very beginning. Sympathetic reassurance but forceful advice can secure the whole-hearted cooperation of the patient—an essential part of the therapy. Don't mince words or conceal facts.

Coronary atherosclerosis, which is today, and probably also was yesterday, the common lot of business and professional men of middle age and older in the U. S. A., may, on occasion, progress so rapidly that an adequate collateral circulation is not developed; or there may be an unfavorable coronary arterial tree to start with. Under such conditions, coronary atheroma, which otherwise may be regarded as no more serious than the graying of the hair, can produce disability and even death. There is a *natural tendency* for recovery to take place in such patients as I. J., owing to the development of collateral circulation, but such restoration of adequate circulation to the part of the heart muscle that is deprived of it does not occur overnight nor in fact in the course of a few days or weeks. One must almost invariably be patient and expect that months and even years may elapse before there is restoration of an adequate circulation. The coronary disease is still there but the evidence of coronary heart disease may subside. It is vital to recognize this normal process of recovery because its existence is largely responsible for the tremendous number of remedies of all sorts that have been introduced in the last several decades and to which undue credit is ascribed. Such remedies include many drugs and even surgical procedures and x-ray therapy.

It is true, of course, that medical treatment is important over the period of symptoms. Such medical treatment should consist in the first place of correction, so far as possible, of the poor regimen of life as well as of a *rest cure*, partial or complete, covering weeks or months at the onset of trouble. The degree of rest naturally depends largely on the degree of the symptoms. In this particular case, it is wise at once to advise a leisurely vacation with very little physical exercise,

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Fatty foods including butter and cream should be used sparingly and rich desserts should be omitted. *Effort* immediately after meals and lying down right after eating should be avoided, as well as effort in cold air, against heavy winds, and on steep grades, but leisurely stairclimbing does no harm. The danger of stairclimbing is an old wives' tale. If these moderate measures of treatment are ineffective and the symptom increases sharply to the point of angina pectoris decubitus (that is, at complete rest) then the patient should remain at complete rest for a few weeks, taking nitroglycerin freely.

*Paravertebral alcohol injection* can be carried out if medical treatment over a period of a few months is unsuccessful and if the pain recurs frequently and is severe, but it must be remembered that such treatment is symptomatic only and that very uncomfortable intercostal neuralgia very often follows for a few weeks. Nevertheless, a few persons have been much helped through the procedure, by getting rid of 95 per cent of the pain which can be so wearing on the nervous system.

#### CORONARY HEART DISEASE: (2) ACUTE MYOCARDIAL INFARCTION

Case VI.—K. L., a banker sixty years old, has been under severe nervous strain ever since the depression and has been unable or unwilling to take reasonable care of his health (this neglect, often but by no means always the case, is especially true of the younger victims of acute coronary occlusion). For several years Mr. L. has had rather mild, waxing and waning angina pectoris on effort. He has used some nitroglycerin off and on, but he has never been severely ill or appreciably incapacitated.

This afternoon, while sitting quietly in his office, Mr. L. began to feel the same substernal discomfort which he had long known on active exercise. It increased slowly but steadily in severity despite two tablets of nitroglycerin taken in the course of ten minutes. Finally, after twenty minutes, when he began to break out in a cold sweat he called for help. The doctor came quickly, found him in mild collapse complaining bitterly of heavy substernal oppression radiating into both arms. He gave him  $\frac{1}{4}$  grain of morphine subcutaneously at once, with but little relief. In the course of twenty minutes he gave him another  $\frac{1}{4}$  grain and then ordered an ambulance to transport him to the hospital where he entered in a semicomatose state one and one-half hours after the onset of the pain. He still complained of dull pain which persisted for another six hours. By midnight he was able to drop off to sleep and in the morning awoke with very little pain left, but with a mouth temperature of 100° F. and a leukocytosis of 15,000, and an electrocardiogram showed an absolutely typical picture of an anterior apical myocardial infarct. His blood pressure which had registered commonly about 140 systolic and 90 diastolic dropped to 100 systolic and 80 diastolic at the time of the acute pain and shock but had returned to 130 systolic and 80 diastolic when he was seen the next morning. There were no other symptoms except for nausea and a little vomiting following administration of the morphine.

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month away in the country to restore his mental equilibrium as completely as possible and to fix the myocardial scar as solidly as it can be fixed. This third month is sometimes unnecessary, but I have found very often that in the case of professional and business men the nervous system is likely to go to pot temporarily after the sudden interruption of an active life, and that it takes longer to restore a normal mental and nervous state in such individuals than it takes for the heart to recover.

The *diet* should be light, at first consisting of five small meals a day. Increase in weight should be carefully avoided during convalescence. In fact, since this particular patient is overweight, as is so often true, gradual reduction of some 10 pounds can be effected to great future advantage. It is unnecessary to institute a program of starvation although for the first day or two little or nothing but fluids in moderation (up to 1200 cc.) should be given. *Tobacco* should be omitted, preferably for good, and the *nervous strain* of business worries and exciting visitors should be excluded during the first month. It is of great importance to discuss with the patient frankly and in considerable detail just what is going on in his heart, with sympathetic reassurance, just as soon as the acute symptoms have subsided, in order to allay unnecessary fears of the patient and to secure his whole-hearted cooperation; I have invariably found such discussion very effective.

#### ACUTE CONGESTIVE HEART FAILURE

**Case VII.**—M. N., an overweight widow aged sixty-four years, has had known hypertension of considerable degree (up to 240 mm. mercury systolic and 130 diastolic) much of the time for the past five to ten years. Mrs. N. has been perfectly well except for slight to moderate dyspnea on effort during the past year. Because of her good health she has disregarded medical advice to reduce her weight and to decrease physical and nervous strain, and in fact to reduce or omit her tobacco. This morning at 1 o'clock, after a fatiguing week and an especially busy day with a hurried dinner, theater party and late supper, she was suddenly aroused by acute dyspnea. She was forced to sit up to get her breath and moved to the open window where she sat in great distress, wheezing and gasping for breath. Finally, after fifteen minutes without relief, she called her maid who summoned her doctor at once. He found her in great respiratory distress with asthmatic breathing, lungs full of moist and squeaking rales, lips cyanotic, pulse regular at 100, and a frequent cough with the raising of a slight amount of frothy pink sputum. Her blood pressure was still elevated at 220 systolic and 105 diastolic.

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digitalis preparations now because some of the proprietary preparations are of the new increased international unit strength, following the U.S.P. XI, and some have maintained the old strength with which we are familiar, and on which most of the dosage recommended in current textbooks is based. No other drugs are needed under the circumstances unless one may wish to use *strophanthin* (or *ouabain*),  $\frac{1}{120}$  grain ( $\frac{1}{2}$  mgm.) intravenously, after the administration of morphine on first arrival when the patient is acutely ill. This is emergency treatment and may safely and wisely be used in the absence of previous digitalis. European, Mexican and South American schools employ this drug in this way and are confident of its great emergency value.

Mrs. N. should, moreover, begin the institution of measures of maintenance of her health. We can do very little about the blood pressure itself but in view of past and impending failure we can advise great care to avoid physical and nervous fatigue. In fact, at the moment a fortnight of *bed rest* is advisable, to be followed by gradual resumption of quiet activity. Also, the *diet* should be lightened to about 1200 calories a day so that the patient may lose weight and avoid overloading her stomach at any one time. *Tobacco* should be omitted since it often tends to raise blood pressure and is a definite irritant to stomach, bronchi and heart, even though it does not itself produce heart disease.

### CHRONIC CONGESTIVE HEART FAILURE

Case VIII.—O. P., a physician seventy years old with a past history of hypertension and myocardial infarction, is seen by a doctor friend at home because of anasarca that has been accumulating for a period of several weeks and which has resisted simple measures of rest and digitalis. There has been no pain or palpitation.

He is found bolstered up in bed with little dyspnea but with slight cyanosis, engorgement of the neck veins, and venous pressure of about 20 cm. of water, a somewhat tender liver edge felt 3 inches below the costal border, and moderate soft edema of both legs to the mid-thighs and of the lower back in the sacral region. The heart is moderately enlarged with normal rhythm, rate 72, and the blood pressure is 170 systolic and 100 diastolic.

This man is in chronic total congestive failure. His past history shows that he has gone through a period of pulmonary congestion with dyspnea followed by myocardial infarction

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1930), is very helpful. Now and then when hydrothorax is present, which was not true in this case, the chest may be *tapped*, and improvement in the condition of the patient will result; 500 to 1000 cc. of fluid may be withdrawn, usually from the right side in such cases.

### PAROXYSMAL TACHYCARDIA

Case IX.—R. S., a nervous young college student of twenty had applied for military service but was rejected because of a paroxysm of tachycardia during the examination. He became very apprehensive and consulted his local physician to determine how much heart trouble he had and what to do about it.

On examination no abnormalities are found. Laboratory tests, including x-ray film and electrocardiogram, are all normal. The patient gives a story of having had for two years occasional attacks of regular racing of the heart, lasting half an hour at a time, making him very uncomfortable and exhausting him for hours afterwards. The attacks have recurred about once every two weeks, particularly when he is tired and after heavy smoking. On two occasions they came as a result of excitement, first of a difficult college examination, and second, of the physical examination for the army.

**Treatment.**—In the first place, complete reassurance is indicated, with a statement to the young man that he may have such attacks off and on for fifty years and still be otherwise in excellent health, in the absence of the development of any other trouble. Heart disease is not likely to occur. If it does, it will be from other causes. However, certain measures should be advised in an attempt to prevent or shorten the attacks themselves:

1. It is wise to restrict *tobacco* to a minimum of a few cigarettes a day or to omit it altogether since *tobacco* has been definitely proved in this patient to be a provoking factor.

2. Reasonable care should be exerted to avoid excessive *fatigue*, nervous and physical.

3. When the attack occurs, firm pressure by the fingers over the *carotid sinus*, preferably on the right side, for a few seconds at a time should be tried, because in about one in ten cases it is dramatically successful in abolishing the paroxysm.

4. *Quinidine sulfate*, 6 grains, at the onset of an attack may shorten spells that would ordinarily last more than half an hour. It does not always work but it is worth trying. Also, *quinidine sulfate*, 3 grains four times a day, may be taken for

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## CONCLUSION

In conclusion, it may be said that the treatment of most of the common forms of heart trouble is simple, quickly learned, and easy to apply, but that two things are essential, first, that the treatment fit the particular case—in other words, that the diagnosis be correct—and second, that much patience and care be exercised by doctor and nurse in carrying out the details of therapy, for what seem to be trifles may on occasion mean the difference between life and death.

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are *sulfanilamide*, *sulfapyridine* and *sulfathiazole*. A new derivative, *sulfadiazine*, is now having an extensive trial and will probably come into wide use in the near future because of its low toxicity and general effectiveness. Each of these drugs has features which distinguish it from the others, both with regard to its effectiveness and to its toxicity. The factors concerning each of these drugs in so far as they relate to the treatment of pneumonia will be considered briefly.

**Sulfanilamide.**—Because sulfanilamide is relatively ineffective in the treatment of pneumococcic pneumonia and has almost no effect in the treatment of staphylococcic or Friedländer bacillus infections, it should not be used to begin therapy in any patient with pulmonary infections. It should be reserved for the treatment of patients with pneumonia only after the hemolytic streptococcus has been established as the etiologic agent. Sulfanilamide has a greater tendency to produce acute hemolytic anemias, as well as a slowly developing anemia when it is used over a long period. Inasmuch as the hemolytic streptococcus likewise tends to produce marked anemias, it is preferable to use sulfapyridine even in cases of infection with this organism. Because sulfapyridine is so poorly tolerated, however, it may be necessary to resort to the use of sulfanilamide. Sulfanilamide has the advantage of being readily absorbed and easily excreted, and it produces a minimum of renal complications. It can be given subcutaneously in an 0.8 per cent solution in physiological sodium chloride, and it is also well absorbed after rectal administration. In the treatment of pneumonia the tendency of sulfanilamide to produce marked cyanosis is a great disadvantage.

**Sulfapyridine.**—Until the introduction of sulfathiazole, sulfapyridine was considered to be the drug of choice in the treatment of all cases of pneumonia. This is due mainly to the fact that it is highly effective in the treatment of pneumococcal infections. It is also highly effective against hemolytic streptococcal infections, but only slightly effective against infections with *Staphylococcus aureus*. About two thirds of all patients who receive sulfapyridine have nausea with vomiting of varying severity. This symptom may be severe enough to make it impossible to continue effective therapy with this drug. It also has the disadvantage of irregular absorption and excre-

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## ETIOLOGIC DIAGNOSIS

**Sputum and Blood Cultures.**—It is generally recognized that early treatment is essential for the best results from either chemotherapy or serum therapy in the treatment of pneumonia. Because sulfonamide derivatives vary in their effectiveness against different bacteria, it is highly desirable to know the causative agent in any case of pneumonia under treatment. It is therefore essential, as soon as a diagnosis of pneumonia is suspected, to obtain materials for this purpose. Sputum should be obtained for culture and pneumococcus typing, and blood should be obtained for culture, preferably before sulfonamides are administered. It is not necessary, however, to wait for the results of these cultures before administration of the drug is begun.

## ORAL CHEMOTHERAPY

**Choice of Drug.**—Of the drugs now generally available, it is obvious from what has been said that sulfathiazole is the drug of choice to initiate chemotherapy in all cases of pneumonia before the etiologic diagnosis is made. Our own present experience would indicate that sulfadiazine is to be preferred. In cases in which the hemolytic streptococcus is strongly suspected as the etiologic agent, as, for example, following a septic sore throat or acute tonsillitis, it is preferable, when sulfadiazine is not available, to start treatment with sulfapyridine. If this drug is poorly tolerated, sulfanilamide may be used.

**Precautions.**—In all patients to whom sulfanilamide derivatives are to be administered *it is important to obtain a history of previous treatment with these drugs.* In particular, inquiry should be made concerning drug rashes and fevers, severe nausea and vomiting or renal symptoms, such as hematuria or anuria. In such patients the drug is administered with the greatest of caution. Patients who have previously had drug fever or drug rash may have a recurrence of these symptoms within a few hours or days after treatment with these drugs is started. This may necessitate stopping therapy or changing to another drug. In patients who have had hematuria or anuria it is important to evaluate the renal function and to ascertain whether there is any blood nitrogen retention,

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**Use of Alkalies.**—All patients receiving *sulfanilamide* should also be given alkalies. These may be administered in the form of bicarbonate of soda, 10 or 15 grains with each dose, or, if parenteral administration is employed, one-sixth molar sodium lactate solution may be given with the clyses. Alkalies are not essential with other drugs, since only *sulfanilamide* produces a reduction of the fixed base in the blood. Some physicians prefer to use them in small amounts, however, such as 5 to 10 grains of sodium bicarbonate with each dose. This is thought to increase absorption from the stomach and to decrease the possibility of renal complications. There is no conclusive evidence that either of these purposes is accomplished.

**Chemical Determinations of Blood Concentration.**—In most uncomplicated cases of pneumonia where there is a rapid favorable response to chemotherapy, it is probably not necessary to carry out chemical determinations. The results of such determinations indicate wide variations in blood levels in spite of the favorable response. In general, the concentrations obtained in the course of treatment with the drugs given in the doses recommended above are about as follows: with *sulfanilamide* and *sulfapyridine*, between 4 and 8 mg. per 100 cc. of blood; with *sulfathiazole* between 2 and 6 mg. and with *sulfadiazine* between 8 and 12 mg. Estimations of blood levels should be made whenever there is vomiting, when the drugs are given irregularly or frequent parenteral doses are used, and also when there is a poor response in spite of full doses without vomiting. In such instances the finding of low blood levels would indicate increasing the dose to obtain appropriate levels or, if high levels are obtained while there is marked nausea and vomiting, a reduction of the dose and an increase in the amount of fluids would be indicated. (See also Precautions, above.)

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The administration of sulfonamides by parenteral routes is indicated whenever there is severe nausea and vomiting or when for some other reason, such as after gastric surgery, oral administration is not desirable. It is also indicated to initiate

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Whenever parenteral therapy is used, it should be discontinued as soon as the patient is able to take the drug orally, and further treatment maintained by the latter route.

#### FURTHER CONSIDERATIONS IN THE CHEMOTHERAPY OF PNEUMONIA

**Duration of Drug Therapy.**—In cases of uncomplicated pneumonia the usual experience has been a clinical response corresponding to a crisis within eighteen to thirty-six hours, or occasionally forty-eight hours, after the beginning of therapy. In such cases the usual doses may be continued for two to five days after the temperature and pulse are normal, and preferably until the leukocyte count has also returned to normal. Drug therapy is maintained for the longer period in the patients who were most severely ill or who were ill for several days before treatment was started. Opinions differ as to the *maintenance dose* after essential recovery. Some physicians prefer to reduce the dose and others prefer to maintain the same dose and stop treatment abruptly. We prefer to maintain the usual doses of sulfapyridine and sulfathiazole. In the case of sulfadiazine the dose may be reduced after a clinical crisis to 1 gm. every six hours until it is stopped.

**Indications for Prolonged Chemotherapy.**—In pneumococcal pneumonia in which there are *purulent complications*, or where there has been a *bacteremia* or *extensive pulmonary involvement*, it may be desirable to continue treatment for some time longer. It is well to remember that the longer therapy is continued the more likely one is to encounter complications, such as drug fever, rashes and leukopenias. In patients who have proved purulent complications, full doses (1 gm. every four hours) may be maintained for a total of ten days or longer, but more prolonged therapy given in the hope of avoiding surgical intervention is not to be recommended. In particular, it is probably not wise to continue chemotherapy in patients who have sterile pleural effusions. Such patients may have low-grade fever and leukocytosis until the fluid is completely absorbed.

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*Extensions.*—Extensions of the pulmonary process during the course of therapy may be associated with elevation of temperature and pulse rate and recurrence of dyspnea. If the leukocyte count has dropped, it may rise again. Sputum may again become rusty or may continue to be so. The physical signs and x-ray give evidence for the presence of the lesion in a new area. In this circumstance the sputum should be re-examined and another blood culture made. The level of drug in the blood should be determined, and if this is low the dose of drug should be increased. It is best, however, to give therapeutic serums if a pneumococcus of a common specific type is found, particularly if there are large numbers seen directly in the sputum or if the blood culture is positive.

*Relapses.*—In some patients, following the initial drop in temperature and pulse rate, signs of resolution appear and the sputum loses its rusty characteristics and becomes purulent. In such an event, if there is a relapse of fever with elevation of pulse and respiratory rates and leukocytosis, there may be a recurrence of the disease in the same lobe. The sputum may again become rusty and the physical signs may indicate only an increase in the amount of solidification in the part of the lung originally involved. The management is the same as in the case of extensions to new areas in the lung.

In some instances there may be some fever associated with the development of *atelectasis* in the resolving lung. This may be indicated by a shift of the trachea or heart borders to the affected side or elevation of the diaphragm on that side. In some cases this may be associated with slight leukocytosis. In the management of this condition it is advisable to encourage coughing and expectoration, and also frequent changes in the position of the patient.

*Drug Fever.*—Drug fever usually occurs after the fifth day of sulfonamide therapy. In patients who have previously received drugs this may occur earlier—even during the first twelve hours. Usually the pulse rate is not altered proportionately, although in severe cases it may be considerably elevated. The appearance of the patient with drug fever does not suggest a recurrence of pulmonary infection, since there is no recurrence of the dyspnea or toxemia. The leukocyte count may or may not rise with the fever. If drug treatment is continued and

*Extensions.*—Extensions of the pulmonary process during the course of therapy may be associated with elevation of temperature and pulse rate and recurrence of dyspnea. If the leukocyte count has dropped, it may rise again. Sputum may again become rusty or may continue to be so. The physical signs and x-ray give evidence for the presence of the lesion in a new area. In this circumstance the sputum should be re-examined and another blood culture made. The level of drug in the blood should be determined, and if this is low the dose of drug should be increased. It is best, however, to give therapeutic serums if a pneumococcus of a common specific type is found, particularly if there are large numbers seen directly in the sputum or if the blood culture is positive.

*Relapses.*—In some patients, following the initial drop in temperature and pulse rate, signs of resolution appear and the sputum loses its rusty characteristics and becomes purulent. In such an event, if there is a relapse of fever with elevation of pulse and respiratory rates and leukocytosis, there may be a recurrence of the disease in the same lobe. The sputum may again become rusty and the physical signs may indicate only an increase in the amount of solidification in the part of the lung originally involved. The management is the same as in the case of extensions to new areas in the lung.

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nococcus is determined or as soon as the positive result of a blood culture is determined, provided that at the time the patient has not already shown marked improvement. In all other patients, but especially in those with bacteremia or with common pneumococcus types, in whom essential recovery has not taken place within twenty-four to thirty-six hours of the beginning of chemotherapy, type-specific serum should be given. Serum may be used as the only therapy in patients who have severe toxic effects soon after chemotherapy is started and before a complete clinical response has been obtained. Serum may also be used to advantage in patients who develop purulent infective complications early in the course of chemotherapy.

**Dosage.**—In severe cases where serum therapy is started early, a total dose of 100,000 to 200,000 units is probably required, and two or three further doses of 50,000 to 100,000 units may be given at eight- to twelve-hour intervals if marked improvement does not occur. The largest doses are reserved for the severest cases. The initial amount may be given after the usual precautions, slowly, as a single injection, either undiluted or diluted with saline. Intramuscular injection may be used, and is indicated particularly in old people in whom it is important to avoid thermal reactions. The larger doses are used in such cases.

#### SPECIAL USES OF CHEMOTHERAPY

There are certain conditions in which acute pulmonary infection is not definitely proved but in which the use of chemotherapy may be desirable or helpful. A few conditions in which it has been used successfully may be mentioned.

**Asthma.**—In patients who have prolonged attacks of acute asthma, in which fever supervenes and in which there appear crepitant rales in addition to the musical rales in the lung, the sulfonamide drugs may bring about marked improvement. This is particularly true in patients in whom the asthma occurs either following or in the course of an acute upper respiratory tract infection. Sulfathiazole or sulfadiazine is to be preferred, and these drugs should be used in full doses. If the temperature and pulse rate decline and there is definite clinical improvement within twenty-four to thirty-six hours, treatment may be

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What caused the diabetes—heredity, obesity, the broken femur, interference with normal exercise, or the inordinate intake of soluble carbohydrate while in bed? Plainly the patient was predisposed to the disease by heredity and obesity and lack of exercise combined with excess calories, particularly carbohydrate, but how about trauma?

Trauma can cause diabetes but only when more than nine-tenths of the pancreas are destroyed. There are four fairly authentic cases of pancreatic trauma preceding diabetes which have come to my notice,<sup>1</sup> but this man did not injure his pancreas and fractures of bones do not directly cause diabetes. Support for this view is so overwhelming<sup>2</sup> that I will not labor this categorical statement, because the evidence has been cited elsewhere. Nevertheless, it is one's duty always to run down the previous history in such a patient and seek to determine when the disease began, and this is what I found.

The patient was injured on November 2, and the records of the hospital that day showed sugar 3 plus in his urine and the blood sugar, fasting, five days later was 162 mg. He was discharged from the first hospital on November 10. In the second hospital the laboratory report during his stay, beginning November 11, also recorded the urinary sugar as "brown" on November 11, although four days later, on November 15, it had become negative. Consequently we have absolute proof of glycosuria while in two hospitals, including a statement of 3 plus glycosuria the day of his accident and five days later a blood sugar at a diabetic level. This was nearly three months before he came to my office, reporting that his first knowledge of his diabetes had been within the last twenty-four hours.

Did the diabetes exist before the accident? Heredity and obesity are only suggestive hints that it did, but other evidence is available.

Cramps in the legs are by no means pathognomonic of diabetes, but in answer to my query when I saw him on February 3, he replied that he had no cramps at that time, but that he did have them before his accident, and so severe as to force him out of bed. There is other evidence of pre-existing diabetes which his subsequent course disclosed.

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TABLE 2  
A BASIC DIABETIC DIET

Food	Unit Portion	Grams in Each Portion				Total Daily Portions	Total Grams		
		Weight	C	P	F		C	P	F
Bread.....	1 slice	30	18	3	..	3	54	9	
Oatmeal.....	1 large	30, dry	20	5	2	1	20	5	2
Orange.....	1	150	15	...	..	3	45		
Vegetables, 3-5%.	1 cup	150	5	2½	..	4	20	10	
Milk.....	¼ pt.	120	6	4	4	1	6	4	4
Cream, 20%.....	¼ pt.	120	4	4	24	1	4	4	24
Egg.....	1	60	..	6	6	1	..	6	6
Meat.....	1 small	60	..	16	10	2	..	32	20
Butter.....	1 square	10	..	...	8	3	..	..	25
Grand total grams (approximate)						C150	P70	F80	
Calories per gram						× 4	× 4	× 9	
Total calories—1600 =						600+	280+	720	

other office visit can be arranged. Even over the telephone, when a doctor calls about a case, I urge beginning treatment immediately. One day I was not specific enough with telephone advice when a hospital bed was not ready and Mr. 19820 went into coma waiting for a bed. I am thankful to say he promptly recovered.

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This case of diabetes was extraordinarily mild. The patient became sugar-free in the second hospital toward the end of his stay without dietetic treatment or insulin. This would hardly have occurred if the diabetes had been of so recent origin as to show 7 per cent sugar within two weeks. Manifestly it had been increased by excess of soluble carbohydrate without insulin. And there is additional evidence, because on May 9 the urine was sugar free and the blood sugar after food was 130 mg. even with the omission of insulin.

*Haec fabula docet:* (1) Impress upon each diabetic patient that he is a health officer for his entire family. (2) Secure a specimen of urine and blood immediately after an accident. (3) When exercise is curtailed, protect all patients from excess carbohydrate. (4) Never ascribe to trauma the development of diabetes in an hereditarily predisposed individual, especially when evidence exists of prediabetic symptoms and signs preceding the accident. (5) Begin the treatment of the disease at once. (6) The trauma in this case may have been a mercy because it led to the recognition of diabetes, and *diabetes unrecognized is uncontrolled!*

#### SHOULD A DIABETIC DRIVE AN AUTOMOBILE?

This is a burning question, but before calling to your attention various individuals to whom the subject is of serious import and certain others as witnesses of safe driving, may I read you abstracts from a report of a Committee of the New York State Medical Society in the New York State Journal of Medicine, pages 739-740, 1941, under *Motor Vehicle Drivers—Medical Examinations:*

"Complete accord has been reached regarding recommendations made to the Motor Vehicle Department of the State in connection with licenses to be issued. All persons applying for an operator's license or renewal of such license must sign a certificate as to whether or not they are suffering from or have ever suffered from any of the following: Here follows a list of diseases in which occurs 'diabetes,' and later, 'Diabetics must furnish certificate that constant care is being supervised.'"

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He entered the hospital and the results of his treatment between May 1 and 10 are shown in Table 4. Each day he was urged to take and did take a considerable amount of exercise in walks about the city, in order to simulate working conditions. It is well never to keep diabetics abed except when bed rest is therapeutically indicated.

TABLE 4

TREATMENT OF A MILD DIABETIC WITHOUT INSULIN (Case 20041)

Date 1941	Sugar in Urine (Per Cent)	Blood Sugar (mg.)	Diet			Remarks
			C gm.	P gm.	F gm.	
Apr. 29	0	160				
May 1- 2	0.4	100 one hour after supper				
2- 3	0	80	152	70	81	
3- 4	0		152	70	81	
4- 5	0	150 one hour after lunch	152	75	100	
5- 6	0		152	87	119	
6- 7	0	150 one hour after food	152	87	119	Extraction of two teeth
7- 8	0		152	101	130	
8- 9	0	150 one hour after food	152	101	130	Temperature ranging up to 99.6° F. due to sinus infection; yet no glycosuria
9-10						

So far as this bus driver is concerned, I feel warranted in telling him that he can return to work for two weeks with the understanding that he report for reconsideration of his case at the end of that time.

Witness: Mr. 17465 developed diabetes at the age of thirty-four years. He is a chauffeur, began insulin in the year 1938, within a month after the onset of his diabetes, and has driven a truck, *not a bus*, thousands of miles yearly. "How do you do it?" "By law I have eight hours off in each twenty-four hours. During the remaining sixteen hours I take four meals."

Ought this man to drive this huge truck? In the course of his stay in the hospital nurses and patients commented upon his reliability. He realizes he is a diabetic. He takes scrupulous

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ported at my office in excellent condition. Diet: carbohydrate 205 gm., protein 104 gm. and fat 122 gm., taking 8 units of crystalline insulin plus twelve units of protamine zinc insulin before breakfast, 8 units of crystalline before the evening meal and 8 units on retiring. The tibial arteries are sclerosed. He has driven about sixteen years and has never suffered injury or injured anyone.

The number of diabetic salesmen, grocery men, doctors (339 in number) and private chauffeurs who drive automobiles long distances, who are temporarily or permanently under my care, is very considerable. Recently 45 per cent of 300 successively questioned diabetic patients entitled by age to drive automobiles reported that they did so. I do not recall that one of my diabetic patients has injured another individual while driving, but of course this does not mean that such injury has not occurred. Nevertheless, to report an automobile accident when the driver is a diabetic is considered *news* and the reason is, I believe, that it is so seldom that such an accident takes place. I have some concrete data relative to diabetics and automobiles which I will now call to your attention.

TABLE 5  
AGES OF TWENTY-SEVEN DIABETICS DYING AS RESULT  
OF AUTOMOBILE ACCIDENTS

Age at Death by Decades	Number of Patients
0-10.....	0
11-20.....	1
21-30.....	2
31-40.....	0
41-50.....	3
51-60.....	9
61-70.....	9
71-80.....	2
80 on.....	1
Total .....	27

Five thousand six hundred and sixty-nine of my diabetics have died, and through the courtesy of Mr. Herbert H. Marks of the Statistical Department of the Metropolitan Life Insurance Company, who has classified these by individual number, not by name, I learn that twenty-seven (0.476 per cent), or one in 210, have died as the result of automobile accidents, but in only four instances was the diabetic the driver of the automobile. Of course this does not include deaths which might have been caused by diabetics who did not die, but of such I recall none.

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## THE SERIOUSNESS OF INSULIN REACTIONS

In Berlin last summer Umber, Gebauer and Schweder<sup>1</sup> reported that 37 per cent of the 14,153 diabetics in the city (3.2 per 1000) and 43 per cent of the 82,788 (3.5 per 1000) Jewish diabetics were taking insulin. In this country there are cer-

TABLE 6  
RAPID CHANGES FROM HYPOGLYCEMIA TO HYPERGLYCEMIA

Time	Diacetic Acid	Sugar in Urine	Blood Sugar (Per Cent)	CO <sub>2</sub> Vol. (Per Cent)	Treatment
4 P.M.	0	0	0.060 C.B.*		
8 A.M.	..	..	0.470 C.B.		
8.30 A.M.	..	..	.....	..	32 units protamine zinc insulin
10.20 A.M.	..	..	.....	..	100 units regular insulin
11 A.M.	..	Red	0.400	9	150 cc. normal saline by hypodermoclysis
11.50 A.M.	..	..	0.310	..	100 units regular insulin
11.55 A.M.	..	..	.....	..	300 cc. normal saline by hypodermoclysis
12.30 P.M.	..	..	0.210	11	
2.30 P.M.	..	..	0.0290	27	1000 cc. normal saline with 50 gm. 50% glucose intravenously
3.30 P.M.	..	..	0.0490		
5.00 P.M.	..	..	.....	..	1000 cc. normal saline intravenously

Within thirty-six hours of entrance this patient was in perfectly good condition.  
\* C. B. denotes capillary blood.

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When I saw this man, whose diabetes was of nearly twelve years' duration, dead in his home, and listened to the story of his sister, I could not force myself to believe that his death was due to an insulin reaction, because it was comparatively sudden and had occurred presumably after the patient had taken food and had been treated quite promptly with carbohydrate. I therefore concluded he must have had either a coronary thrombosis or a cerebral accident, and gave this opinion to the medical examiner who, in turn, gave me permission on the strength of this statement to make a postmortem examination. The autopsy showed that death was caused by *aspiration of vomitus*. Undigested viscid fluid, containing fragments of vegetable matter, was found in his upper respiratory passages. There was also the customary arteriosclerosis of the long-standing diabetic. Unfortunately, at the autopsy, which was carried out at 11:00 P.M., the urine was not examined, but the blood sugar was 200 mg.<sup>4</sup>

It makes no difference whether the patient died directly or indirectly as a result of an insulin reaction; in either event it demonstrates the danger of aspiration which diabetic patients undergo when unconscious.

The blood sugar of 200 mg., determined in blood taken from the right side of the heart three hours postmortem, at first thought would count against an insulin reaction, but new evidence points to the importance of the source of the blood. This importance has been emphasized by Dr. Edwin V. Hill of the Department of Legal Medicine of the Harvard Medical School, who has kindly allowed me to insert a partial abstract of a paper recently read by him in Chicago. In the future evidently blood should be taken not only from the left side of the heart but for comparative purposes it would be well that it be taken from the right side as well.

"Samples of post-mortem blood for glucose determinations should be removed from the left side of the heart if significant errors due to post-mortem diffusion of glucose from the liver to the right side of the heart are to be avoided. The lungs apparently provide an effective barrier to the diffusion of glucose from the right side of the heart to the left. The glucose responsible for the post-mortem rise in glucose on the right side of the heart is liberated by glycogenolysis occurring in the liver. This rise is not observed in fasting animals or in cadavers presenting marked liver damage. If the inferior vena cava of an experimental animal is ligated immediately after death the post-mortem rise on the right side of the heart fails to occur."

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**Case II.**—Around midnight, within a month, I was awakened by a telephone call from the brother of Mr. 4735, whom I first saw July 7, 1925 with a history of diabetes beginning that same month at the age of fifteen years, and a story of his father having died of diabetes at the age of fifty years. He became sugar-free at that time on a diet with a trifle over 30 calories per kg. body weight, carbohydrate 68 gm., protein 62 gm., fat 136 gm., and insulin three times during the day, 5-3-5 units. (Note the low carbohydrate value in the diet of sixteen years ago.) The following January he was reported to have gained 6 pounds, to be sugar-free, and, sad to relate and contrary to what I advised, he was not taking insulin. In October, 1926 he entered the New England Deaconess Hospital in diabetic acidosis, with blood plasma creamy; he was sugar-free six days later under a program of 10-10-10 units of regular insulin. Again in March, 1928 he returned in acidosis, and the following June with appendicitis for which he was operated upon successfully by Dr. L. S. McKittrick.

In 1940 the patient returned again in acidosis, with carbon dioxide 26 volumes per cent, blood sugar 450 mg., nonprotein nitrogen 63 mg.; he required 120 units in the first twenty-four hours to bring the blood sugar to normal, and was discharged a week later with 16 units of crystalline insulin plus 48 protamine zinc insulin, with a diet of carbohydrate 150 gm., protein 82 gm., and fat 100 gm. On January 17, 1940, at a cursory visit, he showed 0.2 per cent glycosuria, blood sugar 50 mg. five hours after breakfast, weight 128 pounds dressed, taking 16 plus 48, and was sent a letter urging reduction of crystalline insulin to 10 units. It appeared then that he had been rescued from diabetic coma by his physician a week earlier.

That midnight of the present episode I learned from his brother and from subsequent talks with his doctors that he had been seen in the afternoon by a physician who, finding him unconscious, considered him to be in diabetic coma, as he had been in the previous January; the physician administered 75 units of insulin and sent him to a hospital. In the hospital he was promptly given 1500 cc. of 10 per cent glucose with 30 more units of insulin. Through various telephone messages I also learned that the urine was not only sugar-free but contained no diacetic acid. Some hours subsequently, following an additional injection of 1000 cc. of salt solution with 10 per cent glucose, the blood sugar was 90 mg., but during the remainder of the day, with repeated injections of salt solution and glucose and adrenalin, the blood sugar rose to over 200 mg. The patient failed to respond and the autopsy on the following day was essentially negative, the pancreas weighing 26 gm.

**Case III.**—Miss 11024 developed diabetes in 1932 at the age of twelve years, and was first seen two months later, with a prominent systolic murmur, confirmed four times in 1934. She was intermittently examined: for instance, May, 1932 with blood sugar 590 mg. and carbon dioxide 21 volumes per cent; in

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driven an automobile early that forenoon. When he was found unconscious in bed Sunday noon the daughter, realizing that he had taken no insulin for two and a half days, gave him 10 units and called a doctor, who was puzzled.

Unable to obtain from the family a clear understanding of the treatment given, I suggested calling the doctor again that I might confer with him. I ordered the administration of 40 units of insulin in the meantime, which was given. Subsequently, in conversation with the doctor, and being impressed by the story of deep breathing of the patient, I suggested 40 units of crystalline insulin as well and arranged for the patient's entrance to the hospital. Upon his arrival the blood sugar was 250 mg., but his unconsciousness was so obviously unlike diabetic coma that my colleague, Dr. Priscilla White, after securing a specimen of blood for analysis, gave in advance of the report of the blood sugar 20 cc. of 50 per cent glucose intravenously followed in twenty-four hours by two intravenous infusions of normal saline containing 10 per cent glucose. However, even before the laboratory report was completed, which, by the way, required on Sunday afternoon but one-half hour, both she and I were convinced that the man was suffering neither from diabetic coma nor insulin reaction, but rather that he had undergone a cerebral accident. All reflexes were absent, both superficial and deep, and although the muscles were flaccid, the right leg turning out in contrast to the left gave a hint of more trouble on that side. As reported, the blood sugar before glucose was given amounted to 250 mg., so that there was no evidence of hypoglycemia, and coma was excluded because the carbon dioxide was reported later as 56 volumes per cent.

As a protective measure, on account of the previous administration of insulin, glucose and salt solution were slowly given intravenously for several hours. You can now see for yourselves that the patient soon will succumb, with all the evidences of a cerebral accident. Despite the pleading of four of us, an autopsy was refused. I have no reasonable doubt of the correctness of diagnosis in this case, but an autopsy always should be obtained. I remember that a few years ago the medical examiner was kind enough to give our group an opportunity to be present at the autopsy following the sudden death of one of our patients, supposedly due to an insulin reaction, but eventually

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His wife knew he had diabetes when she married him, but no one had given her any instruction about the disease or diabetics, and she was quite ignorant of insulin reactions. You can imagine her fright and feelings.

What did we do? First of all, Dr. White and I talked with her separately and reassured her. Second, we gave her a Manual to study and showed her the pictures of our many diabetic boys and girls and their happy families. Third, we asked her to be a missionary and come here this morning to tell you to instruct all of your prospective diabetic brides and benedicts about the vagaries of diabetics. A missionary gains confidence in herself and her cause when promoting it. Fourth, so that you will see the importance of stressing the necessity of a bed-time lunch when any patient uses insulin before an evening meal. In general, we avoid an extra dose at this time for fear of accidents but of course sometimes are forced to resort to it, as in Case No. 13274 of this clinic. Fifth, I was able to arrange an interview for the girl with one of my most exemplary patients, an important executive, who chanced to be in the hospital for removal of plantar warts, which, by the way, require very careful treatment, and he consented to talk with her and tell her about his delightful family of five children, of whom he had the picture by his bedside. Sixth and finally, I prevailed upon the bride to stay to the meeting of the hospital diabetic class so that she could see for herself a group of individuals who were apparently happy, getting on comfortably with their treatment with diet, exercise and insulin and leading useful lives.

I do not expect ever to see these people again or even to learn their names, but they taught me a lesson and I hope it will be useful to you as well.

#### DIABETES OF LONG DURATION AND THE DIFFICULTY OF EVALUATION IN A PATIENT WITHOUT A HOSPITAL STAY

Mr. 13279 is an important executive who discovered diabetes in November, 1921, at thirty-two years of age, within about a month of onset, and reported to me in 1934 that his blood sugar recently had been 480 mg. Under the management of an excellent physician and with the close cooperation of his wife, he has done quite well, although neuritis and bursitis have ap-

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single dose of 12 units of crystalline insulin before breakfast and 8 units of crystalline insulin before his evening dinner.

No change whatsoever was made in his diet, which was approximately carbohydrate 160 gm., protein 80 gm. and fat 100 gm., although occasionally it was supplemented by 10 gm. of carbohydrate. In Table 8 are recorded in sequence the dosages of insulin during his stay.

TABLE 8

TRANSFER FROM REGULAR TO PROTAMINE ZINC INSULIN IN A CASE OF DIABETES  
OF NINETEEN YEARS' DURATION

Day	Insulin	Day	Insulin	Day	Insulin
1	27-5-8-5	5	16 + 20-0-0-0	9	12 + 28-0-8-0
2	27-5-8-5	6	12 + 24-0-0-0	10	12 + 28-0-10-0
3	27-5-8-5	7	12 + 24-0-8-0	11	14 + 28-0-8-0
4	16 + 16-8-4-0	8	12 + 28-0-8-0		

Upon more than one occasion he did complain of discomfort in his chest, but save for the electrocardiogram, which, as you recognize, is not quite perfect, and for the moderate calcification of the arteries in his legs, no serious symptoms or signs were observed. In the concluding letter to his physician, I wrote the following:

"Several things were accomplished, I think by Mr. \_\_\_\_\_'s visit. First, a twenty-year diabetic is not as common today as we can expect five, ten and fifteen years from now when patients will have had the benefit of more experience with insulin and a wider use of protamine zinc insulin enabling them to control the diabetes for the greater part of the twenty-four hours. This fact makes it imperative that one protect a twenty-year diabetic from doing 100 per cent day's work. Such an individual simply cannot do it and last. Therefore, I told Mr. \_\_\_\_\_ that he must curtail his work to 75 or 80 per cent of the full quantity.

"Secondly, such wide variation of the blood sugar between 410 and 120 mg. must be stopped and the only way to do this is to use the sheet anchor of protamine zinc insulin and supplement the same with quick-acting insulin for the daytime. At present I doubt if it would be possible, or at least practical, so to adjust the day that all of this could be given before breakfast. Therefore, Mr. \_\_\_\_\_ was given crystalline plus protamine before breakfast and the insulin before his evening meal, realizing full well that if reactions developed in the late night or early morning, either less protamine should be taken or more carbohydrate and protein food late at night, and if during the day, then the crystalline insulin should be regulated.

"In order not to spoil a whole day's test by taking a large quantity of carbohydrate in addition to the 5 or 10 gm. which routinely must be taken in the late morning, late afternoon and retiring, I suggested he depend upon a few nuts, 30 gm. of peanuts for example, and experiment with them because

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SIMPLE LUNCHEES FOR BETWEEN MEALS AND UPON  
RETIRING

	Carbo- hydrate, Gm.	Protein, Gm.	Fat, Gm.
1. Milk ( $\frac{1}{2}$ pint) 240 cc.....	12	8	8
2. Milk ( $\frac{1}{2}$ pint) 240 cc.....	12	8	8
Egg, one.....	0	6	6
	<hr/> 12	<hr/> 14	<hr/> 14
3. Unceda biscuit, one.....	5	1	0
Cheese, 30 gm.....	0	8	11
	<hr/> 5	<hr/> 9	<hr/> 11
4. Unceda biscuit, one.....	5	1	0
Peanut butter, 30 gm.....	5	9	13
	<hr/> 10	<hr/> 10	<hr/> 13
5. Peanuts, 30 gm.....	5	8	12

## DIABETES OF TWENTY YEARS' DURATION

## A MODEL CASE IN A YOUNG MAN

This alert "red-headed" diabetic gentleman of thirty-seven years, Case 2436, has had diabetes for twenty years and has taken insulin seventeen years. Throughout this period he has adhered to diet, adhered to insulin, and at the end of this time his diabetes is controlled with insulin 12 plus 45-6 units. His heart is of normal size, the electrocardiogram is normal, there is no demonstrable arteriosclerosis of the legs by x-ray, and I told him when he was shown at the College of Physicians that if he only had three children instead of two I would have put him in the seventh edition of the Manual, along with the other young man with diabetes of twenty years' duration who is his counterpart. This man takes a diet of carbohydrate 180 gm., protein 90 gm. and fat 100 gm.; his original weight was 119 pounds, his weight today 139 pounds. He represents faithful treatment based upon the conceptions of diabetes promulgated by Naunyn and Allen and helped by the discoveries of Banting and Best, with the consequent liberalization of diets. He encourages me to continue to follow fundamental truths in the treatment of this disease. I hope you all will have as faithful a patient as a model for your treatment of this disease.

SIMPLE LUNCHES FOR BETWEEN MEALS AND UPON  
RETIRING

	Carbo- hydrate, Gm.	Protein, Gm.	Fat, Gm.
1. Milk ( $\frac{1}{2}$ pint) 240 cc.....	12	8	8
2. Milk ( $\frac{1}{2}$ pint) 240 cc.....	12	8	8
Egg, one.....	0	6	6
	<hr/> 12	<hr/> 14	<hr/> 14
3. Unceda biscuit, one.....	5	1	0
Cheese, 30 gm.....	0	8	11
	<hr/> 5	<hr/> 9	<hr/> 11
4. Unceda biscuit, one.....	5	1	0
Peanut butter, 30 gm.....	5	9	13
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highest evidence of infection and active disease. Look for it in *tuberculous families*. Dr. Miriam Brailey<sup>2</sup> has reported that children of tuberculous parents, once contact has been established, show a mortality from tuberculosis that is 15.6 times the community rate. Look for it in the *racially susceptible*. Dr. Brailey has also shown that the death rate due to tuberculosis in Negro children is three to four times that of white children. Look for tuberculosis among those who care for the tuberculous sick. Badger and Ritvo<sup>3</sup> showed that 5.3 per cent of *student nurses* at the Boston City Hospital developed roentgen evidence of pulmonary tuberculosis. Robbins and Ehrlich,<sup>4</sup> however, showed that only 0.4 per cent of high school students had active lesions. Look for tuberculosis among the *student doctors*. Hedvall<sup>5</sup> reports that 11.3 per cent of medical students at Lund University showed pulmonary tuberculosis. Look among the *aged homeless*, the *workers in dusty trades* and wherever there is known *contact*. If tuberculosis is actively searched for, it will be found in the early stage.

Case I.—K. D., a twenty-seven-year-old laboratory technician, developed an acute respiratory infection with cough and slight expectoration associated with a transient gastro-intestinal infection. There were fleeting bilateral pains in the chest for a few days but no definite evidence of pleurisy could be made out. Roentgenograms of the lungs were negative. Constant laboratory contact with tuberculosis decreed a careful follow-up.

Three months later another x-ray examination of the lungs showed a small, roughly circular infiltration in the periphery of the left first anterior interspace. The patient was hospitalized because of the uncertainty of the diagnosis of this lesion, which was known only to be a recent one. Three weeks of observation at bed rest showed no fever and a pulse rate of 70 to 80. There were no physical signs in the lungs. There was no sputum and the aspirated gastric contents were negative for tubercle bacilli. There was no cough or loss of appetite or weight. The tuberculin test was positive.

Another x-ray examination of the lungs three weeks later showed slight but definite increase in the size of the patient's lesion. A diagnosis of a subclinical tuberculous lesion was made on the basis of a progressive increase in the size of the small x-ray shadow, known to be less than three months old. It was a lesion not yet large enough to produce the usual toxic signs of active tuberculosis. It was judged to be a reinfection or adult type of infection because of the constant exposure of the patient for several years to known tuberculous material in the laboratory. It was felt that this lesion deserved sanatorium treatment in its early and curable stage.

If there is reason from the history of contact to suspect that underlying tuberculosis may be present, let no physical examination be considered complete without a *roentgenogram* of the

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Another x-ray examination of the lungs three weeks later showed slight but definite increase in the size of the patient's lesion. A diagnosis of a subclinical tuberculous lesion was made on the basis of a progressive increase in the size of the small x-ray shadow, known to be less than three months old. It was a lesion not yet large enough to produce the usual toxic signs of active tuberculosis. It was judged to be a reinfection or adult type of infection because of the constant exposure of the patient for several years to known tuberculous material in the laboratory. It was felt that this lesion deserved sanatorium treatment in its early and curable stage.

If there is reason from the history of contact to suspect that underlying tuberculosis may be present, let no physical examination be considered complete without a *roentgenogram* of the



Case III.—C. D., a twenty-four-year-old laboratory technician, in the course of an acute respiratory infection was found to have a shadow approximately 1 cm. in size in the left infraclavicular area. She refused a period of sanatorium care on the plea of necessity, and felt that she could readjust her life and secure the needed rest as she continued her work. Most of her time except her actual working hours was spent in bed. Her general health, weight, temperature, diet and blood were all checked periodically. Chest x-rays were taken every two weeks at first, then every four, and later every six weeks.

No change in the woman's condition or in the character of the process was noted for seventeen months. At that time she reported before her scheduled check-up because she was not feeling as well as usual. For the first time a few fine rales were heard in the left infraclavicular area, and the x-ray showed a small but definite spread of the lesion towards the apex. There was no cough, and no sputum. The blood was normal and the smear showed no change in the ratio of the white blood cells to indicate the x-ray change. The corrected blood sedimentation rate was at a subnormal level. Eight months of sanatorium care brought the infection under control. Six years later only a linear scar remains and there has been no further reactivation at any time.

In this young woman a latent, potentially active process was dormant for seventeen months before it developed into active disease. Her decision was against the best advice. However, it proved advantageous to accept the next best treatment and to follow closely a lesion of which we were suspicious. Her co-operation was secured and the importance of the long-time follow-up is clearly shown.

What sort of clinical supervision is needed to complement the roentgen study of these latent and suspected lesions? It is the type of supervision that is directed towards sustaining the highest level of well-being for the patient. It is preventive medicine which works toward control through maintaining the body defenses against infection. It is a supervision that aims at detecting earliest changes in the character of these suspicious lesions. *Temperature, pulse, weight, blood and urine* are five very tangible and significant indices of the individual's well-being. Of these the pulse is the most delicate record of toxicity. Widely divergent resting and active pulse levels may be an early indication of underlying active infection. Changes upward in the constant level of the resting pulse should be observed with concern and suspicion. Changes downward in the resting pulse should be viewed with optimism.

The *blood* needs careful observation to prevent the appearance of anemias. The maintenance of a high hemoglobin level is beneficial. The *red cell sedimentation rate* is in general increased in the presence of any active infection and is expected

Case III.—C. D., a twenty-four-year-old laboratory technician, in the course of an acute respiratory infection was found to have a shadow approximately 1 cm. in size in the left infraclavicular area. She refused a period of sanatorium care on the plea of necessity, and felt that she could readjust her life and secure the needed rest as she continued her work. Most of her time except her actual working hours was spent in bed. Her general health, weight, temperature, diet and blood were all checked periodically. Chest x-rays were taken every two weeks at first, then every four, and later every six weeks.

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findings. Blood examination showed no anemia. White cell differential counts were normal and contributed no significant information regarding the underlying process. The red cell sedimentation rate was always normal.

The patient's daily routine included all the requirements of her nursing course. However, she managed a mid-day rest for an hour and she was in bed by seven in the evening until the character of her lesion was well established by comparative x-ray studies. Extra, high caloric meals were supplied and rich vitamin adjuncts were added to the diet. Her small apical lesion never showed any progression and slowly receded to a thin fibrotic scar. Six years later a fine scar remained without any further evidence of tuberculosis.

This student contracted what was apparently her primary or childhood infection in adult life but was fortunately endowed with a high constitutional resistance to tuberculosis. In spite of her determination to remain on duty against medical advice, her lesion healed, aided by a regimen which she was careful to observe.

It is quite clear from cases III and IV that it is difficult to evaluate the character of the small x-ray lesion. We must above all things educate the patient to the need of x-ray follow-up of these doubtful shadows. It is fateful to report that these small infiltrations are no more than a "spot on the lung" or an old scar which may be forgotten.

**Case V.**—M. A., a twenty-two-year-old stenographer, had been examined five months previously because of a dragging cold and a bothersome but unproductive cough. The initial roentgenogram of the lungs must have revealed some abnormal shadows, for she was told of an "old spot" which was "harmless" and which she could "forget." She was treated for an acute respiratory infection and told to return if the cough did not clear up promptly.

The cough did clear up promptly but the "spot" did not. Within five months this girl developed an acute tuberculous bronchopneumonia involving more than half of the left lung. The sputum was strongly positive. The early institution of pneumothorax was successful.

The conduct of these small roentgen lesions puts upon the physician a responsibility for periodic x-ray and clinical management which cannot be overestimated. There is as yet no other way of evaluating or controlling these small, latent and suspected lesions.

#### GENERAL PRINCIPLES OF TREATMENT

**Absolute Bed Rest.**—What is meant specifically by this phrase, absolute bed rest? It means what it says, *twenty-four hours a day in bed*. There are no exceptions or privileges if it

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at the end of this month showed complete disappearance of the 1.5 cm. cavity and extensive clearing of the acute exudative infiltration. Bed rest without collapse therapy was decided upon for treatment in view of this excellent result.

This patient had not known what *absolute bed rest* was or what the observance of such complete inactivity could do for her tuberculosis. Such a period of clinical observation established for her a basis for treatment and an index of prognosis.

Sanatorium or hospital care during this period of observation is not absolutely essential but the rest so obtained is in the end usually more satisfactory. Equivalent care can often be instituted in the home. There, however, it is difficult to break the long-standing habits of years. It is often impossible to interrupt the stream of visitors or control the oversolicitous family in order to obtain the rest that comes rarely to the tuberculous patient except through the well ordered routine of a sanatorium. The experience of sanatorium treatment, where routine is the basis of the cure, will always remain an educational asset to the tuberculous patient.

**Diet.**—Food should be appetizing, well cooked, attractively served and contain not only the ingredients of a well balanced meal, but the inducement to eat it. Between-meal high caloric drinks are usually needed. Overeating and overweight are both to be avoided. Vitamin demands and the requirements of an adequate diet are higher when the metabolism is elevated by fever and infection.

*Vitamin* deficiency plays its part in the malnutrition of advanced tuberculosis and vitamins should be amply supplied to patients with early lesions. *Insulin* in 10- to 15-unit doses before meals may, in some patients, enhance the appetite and the carbohydrate consumption.

**Exercise, Education and Leisure.**—Exercise plays no part in the management of the acute and active phases of tuberculosis. Absolute bed rest, with or without collapse, is the order of the day. Later, in treating the patient with a quiescent lesion, there is a need for an equitable distribution of rest and exercise. Exercise when first permitted is qualified to mean time up in a chair with blanket, or a single daily trip to the bathroom. Careful clinical and x-ray observation should accompany a slowly graded increase in privileges. A saunter-  
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beginning of modern concepts in treatment of the disease. "An Intimate Portrait of R. L. S." by Lloyd Osbourne, as well as the poems of Robert Louis Stevenson himself revive in us the extraordinarily buoyant spirit of one physically an invalid from his tuberculosis. These books, and others, may help to impart a new philosophy of leisure into the lives of those who do not understand the preservation of an atmosphere that is conducive to maintaining one's defenses against tuberculosis.

### COLLAPSE THERAPY

Whatever method of collapse is undertaken, its principle is the same: namely, more complete rest locally of the lung itself, by the splinting and immobilization of its action. Ringer<sup>7</sup> has put forth a word of warning that collapse measures can be overdone in the presence of small early lesions and in the very far advanced cases. Collapse of some sort is usually indicated in active tuberculosis with well defined cavity formation. But in almost every case, a trial period of three to four weeks of absolute bed rest should precede the institution of any collapse procedure, as shown in case VI. Collapse measures in the extremely advanced case may, from their mechanical effects, incapacitate the patient more than does the disease itself. Dyspnea, empyema, spontaneous pneumothorax and deformities of posture are to be reckoned with. No collapse measure should be undertaken solely for the sake of doing something to the patient, but it should be early and widely applied when the indications are clear.

**Artificial Pneumothorax.**—What is the ideal lesion for artificial pneumothorax? Is it only the unilateral case with positive sputum and a thin-walled cavity? By no means. The *spreading lesion* in one lung may do well if the cavity in the other is satisfactorily closed by pneumothorax.

**Case VII.**—M. M., a twenty-eight-year-old stenographer with far-advanced tuberculosis, gave a history indicative of a recent rapid extension of a lesion that must have been active for several months. Treatment had consisted of desultory home care without good bed rest. When the patient was first seen, physical and x-ray examination revealed a cavity in the right infraclavicular region, with mottling throughout the upper half of the lung. An acute bronchogenic extension, exudative in type, was present in the lower half of the right upper lobe. This was verified by showers of medium coarse rales low down beneath the left breast anteriorly. The patient was acutely ill.

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**Case IX.**—E. M., a thirty-five-year-old married woman, presented a long history of tuberculosis. Moderately advanced disease with a 4-cm. cavity in the middle of the right lung had healed apparently spontaneously on semi-bed rest, four years previously. Reactivation of the disease occurred in the left lung two years later and fourteen months of the same semi-bed rest did not prevent the infection from progressing slowly. A 3-cm. cavity was present in the periphery of the left mid-chest when the patient was first seen. Pneumothorax produced a 40 to 50 per cent collapse but the cavity was held widely open by multiple adhesions to the chest wall. After cutting adhesions on two occasions the cavity was freed of its lateral adhesions but remained open near the left hilar region. Firm diaphragmatic adhesions were noted on fluoroscopy and a left phrenicotomy was recommended and performed. A good elevation of the left diaphragm was obtained. Relaxation of these basal adhesions brought complete closure of the cavity.

Experience teaches that one cannot foretell from the physical examination or the chest x-ray whether adhesions between the pleural surfaces will prevent the induction of a satisfactory pneumothorax. Jennings and his associates<sup>8</sup> report that 24.2 per cent of their 1027 patients thought to be candidates suitable for pneumothorax could not be given air because of adhesions. It is of further interest that only 30.3 per cent of their group with unilateral lesions obtained a satisfactory collapse of the lung without the assistance of other surgical procedures. No benefit was received from pneumothorax in a total of 57.9 per cent of Jennings' cases, either because of obliterating pleurisy or because of unsatisfactory collapse. In this group it was found after three years that three out of four patients who had received no further collapse measures were dead. In contrast, only one out of four of those patients for whom further collapse procedures were instituted when pneumothorax failed, had succumbed.

The true value of any therapeutic procedure is measured by the number of individuals whom it restores to a normal working life. In Jennings' cases with satisfactory collapse, 81.9 per cent were working one to twenty years later. In the partly satisfactory cases, 56.8 per cent were working, but in the unsatisfactory pneumothoraces only 23.1 per cent were working one to twenty years later. It is clear from these figures that when pneumothorax can be satisfactorily induced, with closure of the cavity and with the sputum free of tubercle bacilli, it is a very successful method of treatment. But if pneumothorax cannot be satisfactorily given, even with the assistance of

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consideration before its induction. The benefits of a successful pneumothorax are great. The procedure should be available to all who need it, but its promiscuous use should be curtailed.

### CONCLUSIONS

In our determination to "close that cavity" by whatever procedure may be necessary, let us remember the patient as an individual and recall the character of the disease from which he suffers.

In the treatment of tuberculosis the majority of patients handle their infection well if they observe the basic principle of *absolute bed rest* or rest in conjunction with appropriate collapse therapy. There is another small group of patients with active disease who cure their tuberculosis whether or not they observe the rules of treatment. This may be heresy to the phthisiologist but it is a fact. These fortunate individuals are endowed with a high familial or racial resistance to this disease. A third, not so small group, goes on to progressive and destructive tuberculosis no matter what treatment may be prescribed. These have a chronic and recurrent acute tuberculosis. These individuals are apparently endowed with very little constitutional resistance to their infection. Conservative care, with studious application of the general principles of treatment, may make life more bearable for these patients than extensive surgery. Vigorous measures of collapse in the extremely ill may hasten their demise, too often because the varied systemic expressions of tuberculosis have been overlooked in the effort to conquer the pulmonary involvement. Collapse of the lung can do its local job well, but it is only one phase of the general principles of the treatment and management of tuberculosis.

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The clinical picture may resemble pulmonary tuberculosis, but tubercle bacilli cannot be found in the sputum. On physical examination the apices of the lung are not usually involved, the lower lobes being principally affected.

The presence of bronchiectasis, the stage of the disease and the location of the distended bronchi can be readily and easily determined by the injection of lipiodol into the bronchial tree, for which the supraglottic method is the simplest and most convenient.



Fig. 156.

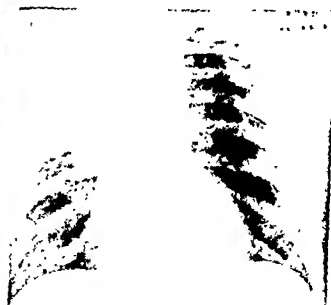


Fig. 157.

Fig. 156 (Case I, E. P.).—Left lateral roentgenogram showing saccular bronchiectasis.

Fig. 157 (Case II, F. C.).—Carcinoma of the right upper lobe bronchus with extension into the lung parenchyma.

Case I (Fig. 156).—E. P., a twenty-two-year-old white, single female, was admitted with a seven-year history of cough, expectoration of 3 ounces of yellow sputum, occasionally blood-streaked, and an afternoon temperature. The family history was negative for pulmonary tuberculosis. The sputum was persistently negative for tubercle bacilli, including gastric analysis and concentration tests. The sedimentation rate was 4 H.L. (Cutler Method).

Bronchiectasis was suspected because of the persistent negative sputum, excessive expectoration, and physical findings. Lipiodol injection proved the diagnosis of *Bronchiectasis* involving the right and left lower lobes.

The patient was discharged with the diagnosis of *Nontuberculous Bronchiectasis*.

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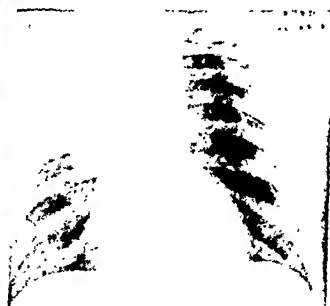


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A fractional percentage of the lung abscesses follow bronchopneumonia and aspiration of foreign bodies. Lung abscess is a disease of symptoms rather than physical signs.

Important in the diagnosis are a careful history and physical examination, serial roentgenograms, including roentgenograms following lipiodol injection, and thorough fluoroscopic examination, in addition to sputum results and tuberculin test.

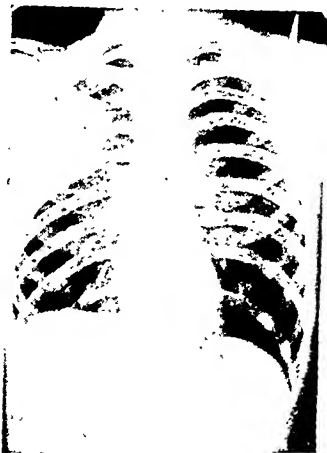


Fig. 158.

Fig. 158 (Case III, W. S.).—Lung abscess with cavity in right upper lobe with fluid level.

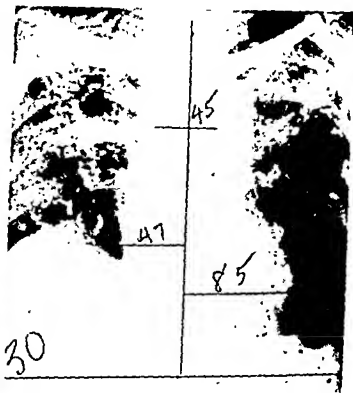


Fig. 159.

Fig. 159 (Case IV, A. T.).—Roentgenogram showing multiple nodular areas of fibrosis extending from the periphery to hilum. Note adhesions and elevation of the right diaphragm.

**Case III** (Fig. 158).—W. S., a thirty-eight-year-old white, single male, was admitted with a two months' history of cough, expectoration of 4 ounces of foul, yellow-greenish sputum daily, loss of appetite and weight. The sputum was persistently negative for tubercle bacilli, and the sedimentation rate was 30 V.C.

The patient was placed on postural drainage, and 300 to 500 cc. of foul sputum was expectorated daily. The patient was discharged with a diagnosis of *Nontuberculous Lung Abscess*.

### PNEUMONOCOINOSIS

It has been recognized that certain dusty occupations commonly give rise to pathological conditions of the lung simulating pulmonary tuberculosis. Four important groups have differentiated:

A fractional percentage of the lung abscesses follow bronchopneumonia and aspiration of foreign bodies. Lung abscess is a disease of symptoms rather than physical signs.

Important in the diagnosis are a careful history and physical examination, serial roentgenograms, including roentgenograms following lipiodol injection, and thorough fluoroscopic examination, in addition to sputum results and tuberculin test.

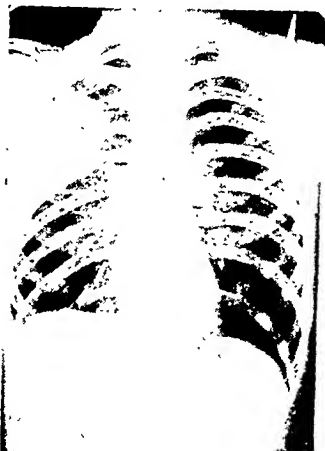


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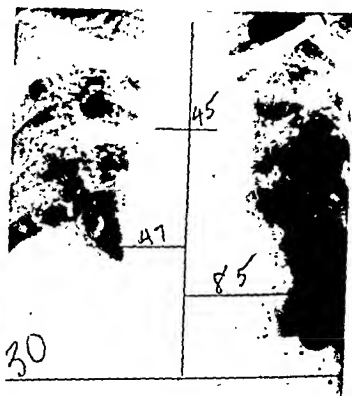


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### PNEUMONOCOCONIOSIS

It has been recognized that certain dusty occupations commonly give rise to pathological conditions of the lung simulating pulmonary tuberculosis. Four important groups have differentiated:

**Case V (Fig. 160).**—M. K., a seventeen-year-old white schoolgirl, was admitted with a one year's history of cough, attacks of dyspnea at night, and some loss of weight. The sputum was persistently negative, the sedimentation rate 3 H.L., the tuberculin test negative and the blood picture essentially negative except for an 8 per cent eosinophil count.

While in the hospital the patient's attacks of nocturnal dyspnea were relieved by adrenalin. The patient was discharged to the *Asthma Clinic* as *Non-tuberculous*.

### DIABETES MELLITUS

The onset of diabetes mellitus is often insidious. The patient gradually notices that he drinks more fluids and passes more urine than normal; or he may complain of weakness, fatigue



Fig. 160.

Fig. 160 (Case V, M. K.).—Lung fields within normal limits for age. Note voluminous shape of chest.



Fig. 161.

Fig. 161 (Case VI, J. G.).—Lung fields within normal limits for age.

and loss of weight rather than any alteration in his urine. In the more severe type of case the onset may be quite acute, with the characteristic symptoms of great thirst, frequent and abundant micturition, usually a very large appetite, weakness and loss of weight. In the very severe cases the first symptom may be coma.

A mistaken diagnosis between diabetes mellitus and pulmonary tuberculosis can be avoided by a careful examination of the urine for sugar, estimation of the blood sugar, sputum examinations, tuberculin tests and serial roentgenograms.

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A mistaken diagnosis between diabetes mellitus and pulmonary tuberculosis can be avoided by a careful examination of the urine for sugar, estimation of the blood sugar, sputum examinations, tuberculin tests and serial roentgenograms.

either at the second or third intercostal space between the nipple and the anterior axillary lines.

Roentgenograms and bacteriologic examination of the aspirated material should easily confirm the diagnosis.

**Case VII (Fig. 162).**—E. H., a twenty-nine-year-old white male, was admitted with a three weeks' history of sharp pains in the left chest, weakness, fatigue and loss of weight. His local physician made a diagnosis of tuberculous empyema after he had aspirated a yellow-green, purulent fluid from the left chest. The sputum was consistently negative for tubercle bacilli, the sedimentation rate 26 D.C., the tuberculin test negative, and the leukocyte count 22,800, of which 87 per cent were polymorphonuclears.

An abscess extending into the subpectoral region was incised and drained. About 16 ounces of greenish, odorless pus was obtained which showed short-chain streptococci. The patient made a complete recovery, and was discharged with a diagnosis of *Nontuberculous Chest Wall Abscess*.

### AMEBIC DYSENTERY AND ABSCESS

Amebic dysentery is caused by infection of the colon by a protozoon known as the *Entamoeba histolytica*. The onset of amebic dysentery is sometimes extremely insidious, the first symptom usually being attacks of diarrhea or alternating diarrhea and constipation, tenesmus and bloody mucous stools.

In the majority of cases, amebic hepatitis is accompanied by pyrexia, leukocytosis, pain in the right hypochondrium, and occasional pains over right shoulder. Pulmonary involvement takes place by the liver abscess rupturing through the diaphragm into the pleural space. The inflammatory reaction may take the form of a severe pleural reaction with fluid formation.

As the condition progresses, a bronchial communication may be established. The diagnosis of the affection can be made without difficulty by laboratory examination for the presence of the parasites in the feces.

**Case VIII (Fig. 163).**—A. M., a forty-three-year-old white male, was admitted with a three weeks' history of chills, fever, night sweats, weakness and dyspnea. The sputum was persistently negative for tubercle bacilli, the sedimentation rate was 31 D.C., the temperature ranged from 100° to 104° F., and there was a leukocyte count of 12,900, of which 61 per cent were polymorphonuclears, 23 per cent lymphocytes, and 16 per cent monocytes.

Right-sided thoracentesis was performed because of dyspnea and the presence of a pleural effusion. About 1000 cc. of clear, straw-colored fluid was removed, and air replacement was made.

After several days the patient's condition became progressively worse, and he expired.

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After several days the patient's condition became progressively worse, and he expired.

Cases of this type present a good deal of difficulty in arriving at a diagnosis. Repeated heart examination for the presence of a murmur, fluoroscopic examination and roentgenograms to note the size and shape of the heart and condition of the lungs, together with sputum examination, are essential to a correct diagnosis.

Of course, it must be remembered that pulmonary tuberculosis and mitral stenosis may occur in the same individual. We have two such patients in the Sanatorium at present.

**Case IX (Fig. 164).**—J. S., an eighteen-year-old white male, was admitted with a six months' history of frequent hemoptyses ranging from 1 to 5 ounces, weakness, dyspnea and chest pain. The sputum was persistently negative for tubercle bacilli, the sedimentation rate was 22 D.C., and the tuberculin test was negative.

Examination of the heart revealed the presence of a presystolic thrill over the mitral area, enlargement on percussion, and systolic and presystolic murmurs at the apex.

The patient was discharged to the *Cardiac Clinic* with a diagnosis of *Mitral Stenosis*.

#### DUODENAL ULCER

Before "blood spitting" is regarded as an indication of pulmonary tuberculosis, one must at least be sure that the blood really comes from the lungs and not the gums, nose, or stomach. The description given by a patient is very often unsatisfactory or misleading.

In *hemoptysis*, the patient coughs up the blood, which is often frothy and mixed with sputum. The blood is alkaline in reaction, and tubercle bacilli or elastic fibers may be detected. The patient usually gives a history of cough. In *hematemesis*, the patient vomits blood which is not frothy and is often mixed with vomitus.

The blood may be acid from admixture with gastric juice, and tubercle bacilli will be absent. The patient usually gives a history of abdominal distress after meals.

**Case X (Fig. 165).**—A. Z., a thirty-four-year-old white female, was admitted with a year's history of slight cough, "spitting up" of blood on several occasions, weakness, abdominal discomfort after meals, and loss of weight. The sputum was persistently negative for tubercle bacilli, the sedimentation rate was 10 H.L., and the benzidine test on feces was positive.

A roentgenographic series was reported as consistent with *Duodenal Ulcer and Intestinal Stasis*, consequently the patient was discharged as *Nontuberculous* to the Gastro-intestinal Clinic.

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29 V.C., and the leukocyte count 17,500 with a normal differential count. The patient's temperature ranged from 99° to 103° F.

In view of the negative sputum, serial roentgenograms and physical findings limited to the lower two-thirds of both lungs, monilia infection was suspected. Sabouraud's media revealed the presence of a pure culture of *Monilia albicans*, *Parasaccharomyces* A. In addition, the bacteriologic examination of the sputum showed hemolytic streptococci.

Despite iodide therapy both by mouth and by the intravenous route, prontosil, transfusion and administration of oxygen, the patient expired.

#### *Autopsy Report*

##### *Anatomic Diagnosis:*

Bronchiectasis with Abscesses of Right and Left Lower Lobes  
Bronchopneumonia Upper Lobes  
Bilateral Fibrous Pleuritis

##### *Microscopic Diagnosis:*

Monilia Infection

### RHEUMATIC PLEURAL EFFUSION

Acute rheumatism may be a cause of pleurisy with effusion. It may occur after a history of joint pains or the symptoms of acute rheumatism, such as chorea, recurrent tonsillitis, pericarditis and endocarditis. In such cases the diagnosis is not difficult; it is less easy when the pleuritic effusion is itself the main sign.

The absence of previous ill health, of abnormal apical signs, negative sputum examination for tubercle bacilli, negative family history for tuberculosis, the presence of cardiac murmurs, the rapid onset of the disease, and the almost equally rapid resolution of the effusion are points in favor of rheumatism rather than tuberculosis. Guinea-pig inoculation of the chest fluid is also of importance in arriving at a diagnosis.

**Case XII (Fig. 167).**—G. P., a thirty-five-year-old white male, was admitted with a six weeks' history of dyspnea, weakness, cough, pains over the right chest, and joint pains. The sputum was persistently negative for tubercle bacilli; sedimentation rate 25 D.C.; blood pressure 190/100. The urine showed a heavy trace of albumin with many red cells and occasional casts; the blood picture showed a moderate degree of anemia.

Right thoracentesis was performed and the fluid on guinea-pig inoculation was negative for tubercle bacilli. Cardiac enlargement was made out on percussion, and systolic and diastolic murmurs were audible at the apex.

The patient was discharged to the Cardiac Clinic with a diagnosis of:

Rheumatic Pleural Effusion  
Rheumatic Heart Disease  
Hypertension  
Glomerular Nephritis

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Rheumatic Heart Disease  
Hypertension  
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After three years of x-ray treatments at Pondville, the patient died.\*

*Autopsy Report*

A. *Hodgkin's Disease*, involving lungs and pleura, cervical and mediastinal glands, spleen and skin.

B. *Amyloid Disease*, involving liver, spleen, adrenals and kidneys.

POSTPNEUMONIC EMPYEMA

The differentiation between streptococcal, pneumococcal and tuberculous empyema is essential because the treatment differs.

The formation of purulent effusions is a rare occurrence in early tuberculosis, and only exceptionally does it appear idiosyncratically as the initial sign of the disease. It does not occur with anything like the frequency of serous pleural effusion.

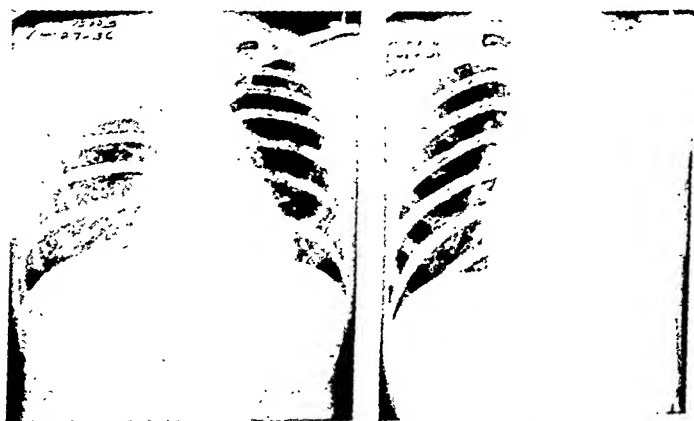


Fig. 168.

Fig. 169.

Fig. 168 (Case XIII, E. S.).—Density of upper third of right lung.

Fig. 169 (Case XIV, W. C.).—Left-sided hydrothorax.

Tuberculous empyema is frequently associated with pulmonary tuberculosis, and may occur either insidiously as a serous effusion that gradually becomes more and more purulent, or follow rupture of a pleural cavity into the pleural space, or it may occur by ulceration of a caseous focus.

A correct diagnosis can be made by obtaining a careful history, frequent roentgenograms, sputum examinations, diag-

\* We are grateful to Dr. Parker, Superintendent of the Pondville Hospital, for the subsequent history and autopsy findings on this case.

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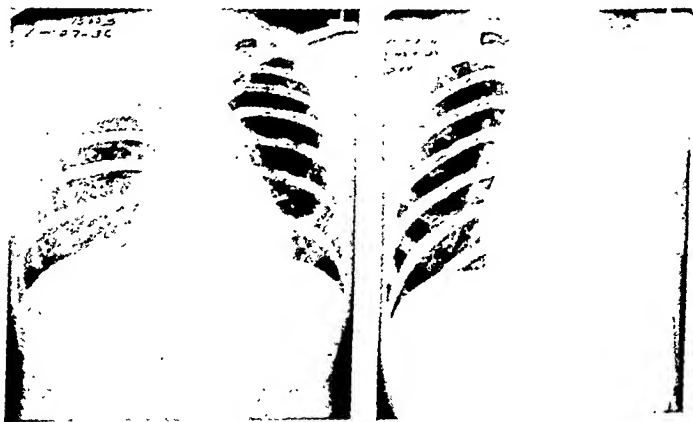


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Under a period of observation the patient did extremely well. She became asymptomatic. Physical findings which were present at the right base cleared. Serial roentgenograms also showed clearing, hence the patient was discharged with the diagnosis of *Nontuberculous Resolving Bronchopneumonia*.

### LYMPHATIC LEUKEMIA

Although pulmonary tuberculosis is the first disease that should be ruled out in any case of pleural effusion, nevertheless there are other conditions which can account for the effusion.

Severe blood diseases may give rise to inflammation of any of the serous membranes and thus lead to ascites, pericarditis, or

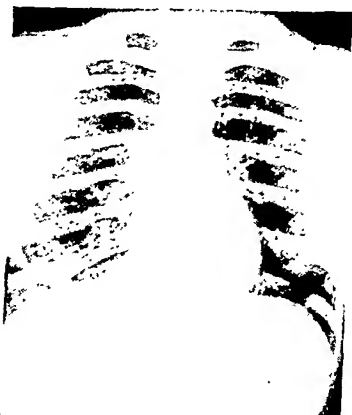


Fig. 170.

Fig. 170 (Case XV, V. R.).—Bronchopneumonic patch at right base.



Fig. 171.

Fig. 171 (Case XVI, S. McC.).—Right-sided hydrothorax.

pleurisy with effusion. The latter is seldom an early symptom in such cases, however, and the diagnosis can be made on the basis of pronounced anemia, glandular, splenic and hepatic enlargement, gland biopsy, and pathologic blood changes.

Roentgenograms and sputum examinations should help in differentiating the condition from pulmonary tuberculosis.

**Case XVI (Fig. 171).**—S. Mc., a sixty-seven-year-old white, single female, was admitted with a three months' history of a dry cough, increasing weakness and dyspnea. Sputum was consistently negative for tubercle bacilli. Blood count: red blood cells 2,980,000; hemoglobin 60 per cent; white blood cells 300,000, with 95 per cent lymphocytes, the greater number of which were of the small variety, and 5 per cent polymorphonuclears. The liver and spleen were markedly enlarged.

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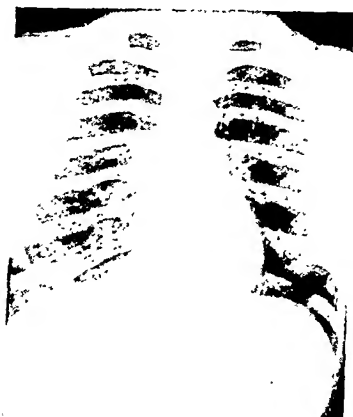


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remote effects, the various manifestations are readily classified. There are three distinct bacteriologic types: *mitis*, *intermediate* and *gravis*, all of which are virulent by the guinea-pig test. All give off a toxin which is neutralized by the antitoxin available to physicians.

**Symptoms.**—The milder types of diphtheria usually give rise to a comparatively slow development of symptoms with heavy membrane formation, while the *gravis* type is apt to be fulminating from the start, with much edema, often hemorrhagic manifestations, and may kill before the membrane has had time to become thick. However, the degree of natural resistance offered by the patient may allow a *mitis* strain to advance rapidly or a *gravis* strain to be held in abeyance. Furthermore, the part invaded is of great importance. This applies particularly to the nose.

Infections confined to the *anterior nares* appear to give rise to minor local lesions and only rarely to remote evidences of toxin absorption. On the other hand, involvement of the *post-nasal space* gives rise to a high incidence of myocarditis.<sup>1</sup> It is by no means an easy matter to recognize these nasal forms of diphtheria; but in the event of a possible exposure, and especially during the convalescence of scarlet fever when latent diphtheria organisms may be activated, one should always keep in mind the possibility of nasal diphtheria and take cultures.

In *faucial* diphtheria the membrane formation is the clue to diagnosis. It is accompanied by edema and enlargement of the tonsils. The membrane spreads beyond the confines of the tonsils to the pillars, the uvula and soft palate, and to the posterior pharyngeal wall. When removed, it leaves a bleeding surface, and it will not mash as does the yellow exudate of follicular tonsillitis because the membrane is made up largely of fibrin. If advanced, there is a characteristic odor which may pervade the room.

Local measures consist of attempts to soothe and clean the throat. The most effective of these is a warm 10 per cent dextrose irrigation. Loeffler's solution and other more powerful applications, such as silver nitrate, are now obsolete. Any measure which injures the mucous membrane favors the growth of the bacilli. This principle applies to all other acute throat infections, especially of streptococcal origin.

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tends to produce apathy. It is dangerous to mask any symptoms of airway obstruction. Restlessness, increased respirations and cough are the earliest indications of obstruction. Opiates and other sedatives tend to mask these symptoms. Even as the membrane tends to become loosened under the influence of antitoxin, obstruction may be suddenly brought about.

### DIPHTHERIA—MEMBRANOUS STAGE

DIPHTHERIA—MEMBRANOUS STAGE				
Fundamental Pathology	TOXEMIA. Disturbed carbohydrate metabolism. Hypoglycemia merging into hyperglycemia in prolonged toxemia. Gradual or sudden vascular collapse with low blood volume in the heart chambers. Early parenchymatous hyaline degeneration of myocardium.			
Onset	Fulminating or smoldering.			
Signs and Symptoms	FEVER. TACHYCARDIA. Edema. Lymph logging. Pasty look. Apathy.	Vomiting. Gradual development of systolic murmur. Extrasystoles. Gallop rhythm. Cyanosis with mottling. Convulsions.		
Common Complications	Respiratory obstruction. Nephritis.			
Treatment	ANTITOXIN—intramuscularly or intravenously or both:			
	Weight of Patient		Type of Disease	
			Mild, Units	Moderate, Units
				Malignant, Units
	Under 50 lbs.....		5,000	10,000
	Over 50 lbs.....		10,000	30,000
				50,000
				100,000
	INTRAVENOUS DEXTROSE 10% except in mild cases, both as prophylactic and for treatment of circulatory failure. Repeated every 8, 12 or 24 hours.			
	Dislodging of membrane dangerous with lowered cough reflex.			
Signs of respiratory obstruction not to be confused with those of circulatory failure.				
Restlessness, increased respiration and cough calls for suction of supraglottic area rather than medication.				
Avoid morphine.				
Intubation or tracheotomy for laryngeal obstruction.				
Electrocardiograms.				

No drug of the *sulfonamide* group has as yet been found to be of any value in diphtheria. *Alcohol* is not indicated. That it is well tolerated is no logical reason for its use. *Strychnine* has never been shown to be effective in any careful clinical test. The use of *digitalis* needs careful consideration. An undam-

tends to produce apathy. It is dangerous to mask any symptoms of airway obstruction. Restlessness, increased respirations and cough are the earliest indications of obstruction. Opiates and other sedatives tend to mask these symptoms. Even as the membrane tends to become loosened under the influence of antitoxin, obstruction may be suddenly brought about.

### DIPHTHERIA—MEMBRANOUS STAGE

Fundamental Pathology	<b>TOXEMIA.</b> Disturbed carbohydrate metabolism. Hypoglycemia merging into hyperglycemia in prolonged toxemia. Gradual or sudden vascular collapse with low blood volume in the heart chambers. Early parenchymatous hyaline degeneration of myocardium.		
Onset	Fulminating or smoldering.		
Signs and Symptoms	<b>FEVER.</b> <b>TACHYCARDIA.</b> Edema. Lymph logging. Pasty look. Apathy.	Vomiting. Gradual development of systolic murmur. Extrasystoles. Gallop rhythm. Cyanosis with mottling. Convulsions.	
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## VASOMOTOR COLLAPSE

Fundamental Pathology	Postdiphtheritic polyneuritis. Paralysis of motor end-plates of parasympathetic nerves.	
Onset	Sudden, with lowering white blood cell count, a relative lymphocytosis, and low blood pressure.	
Signs and Symptoms	Pallor, marked. Frightened look. Cold skin. Splanchnic relaxation. Low blood volume of heart.	Oligemia. Epigastric pain. Vomiting. Enlarged liver.
Treatment	Pitressin, 0.25 to 1.0 cc. subcutaneously or Paredrine hydrobromide 0.25 to 1.0 cc. intramuscularly. Fluid intake increased by mouth or intravenously. Warmth. Abdominal binder. Morphine for restlessness.	

## OTHER POSTDIPHTHERITIC PARALYSES

General Features and Management	Palatal paralysis: regurgitation of fluids through nose may necessitate nasal tube feedings. Strabismus and paralysis of accommodation: clear up almost invariably without treatment. Respiratory paralysis: respirator promptly. Polyneuritis: orthopedic and neurologic consultations regarding supports, massage and reeducation of muscles.
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## NEUROGENIC IRRITABILITY

Fundamental Pathology	Sinus node. Parasympathetic nerves. Vagus.
Onset	Insidious.
Signs and Symptoms	Evening tachycardia. Relative tachycardia or bradycardia. Irritable heart.
Treatment	Very gradual resumption of activity.

support observed is more likely due to the intravenous dextrose which is part of their routine.<sup>2</sup> Sufficient digitalis to augment cardiac action could well precipitate or increase heart block. Sound clinical evidence of the value of digitalis in diphtheria is lacking. The theoretical disadvantages favor avoiding its use. This conforms to the present feeling of distrust in the routine use of this drug in pneumonia, influenza and typhoid fever. My own experience does not permit me to place any reliance what-

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pooled convalescent serum when given early is more prompt and dramatic in its neutralizing effect than is antitoxin in diphtheria. The temperature drops abruptly, the rash fades, and the inflammation in the throat subsides. Statistics show that the incidence of complications is appreciably reduced by the use of serum.<sup>7</sup> However, this reduction is only relative because the pyogenic properties of the streptococcus are not sufficiently thwarted.

**Sulfanilamide Therapy.**—Sulfanilamide is particularly effective against beta-hemolytic streptococci. Thus it is that we now have a second valuable specific in this disease. At the very outset we must emphasize that this drug does not influence the manifestations of the toxin. Sulfanilamide does not reduce or shorten the initial fever or blanch the eruption. This is clearly established by all the properly controlled clinical tests. If given only for the duration of the eruptive stage it will not even be as effective in reducing complications as serum treatment alone. On the other hand, if given in adequate dosage at the onset, and if a maintenance dosage be continued for three weeks, the incidence of complications will be greatly reduced.<sup>8, 9</sup> There is no longer any doubt whatever in my mind on this point.

**Reactions.**—The only question which arises regarding the routine use of this drug in scarlet fever is whether the dangers from its continued use over three weeks in mild cases are less than the dangers without its use. Certainly all sorts of complications can arise in the convalescence of the mildest cases, and many factors influence the incidence of these complications.<sup>7</sup> Severe reactions from this drug in scarlet fever are rare. Anorexia, vomiting, rashes and drug fever are easily checked by discontinuing the drug. Anemias may be sudden, severe, and dangerous, but they are rare. If these are weighed against the incidence of severe pyogenic complications in the untreated cases, the balance is well in favor of the routine use of the drug.

This leads to another question. Should routine sulfanilamide treatment be carried out *in the home* for three weeks? There are those who encourage this, assuming supervision to be the same as in a hospital. But the cost of such home treatment with blood examinations and daily visits throughout convalescence is apt to exceed the cost of hospital care. Without proper supervision the danger of routine sulfanilamide treatment takes on

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days of chemotherapy, ethmoiditis took care of itself better than did the infections of the other sinuses.

*Cervical adenitis* may subside without suppuration. I have yet to be convinced that either heat or cold applied locally alters the course of the process, although either may be of considerable comfort to the patient. If suppuration does occur it should be given time to come very close to the surface, when a small incision is made not to exceed 1 cm. On the other hand, if the suppurative gland is deep and shows signs of burrowing a surgeon skilled in this field should be called. Antitoxin therapy is of no avail in late pyogenic infections because the toxin is not responsible. In cases beginning with general sepsis immunotransfusion is indicated along with sulfanilamide.

**Diet.**—The diet in scarlet fever depends entirely on the severity of the symptoms. Mild cases are restricted to soft solids, while patients with a temperature above 101° F. are given liquids with abundance of fruit juices. High cod liver oil concentrates have not proved effective in reducing the incidence of otitis media.<sup>11</sup> As the fever recedes the diet is increased to soft solids, and when the temperature returns to normal the diet should be the normal diet for the age of the patient. Avoidance of meat and eggs during convalescence is contrary to established clinical data.

**Nephritis in Scarlet Fever.**—The idea that *acute glomerulonephritis* is due to faulty diet is now obsolete. This complication appears to be due to a violent antigen-antibody reaction.<sup>12</sup> A fruit juice diet with cereals is indicated. In the event of *vomiting*, intravenous saline not only overcomes dehydration but serves as the safest diuretic. The symptoms of uremia must not be confused with those due to *cerebral edema* which calls for magnesium sulfate by mouth in doses of from 1 to 2 ounces (30 to 60 cc.) of a 50 per cent solution. In emergency it may be given intramuscularly, 0.2 cc. of a 25 per cent solution per kilogram of body weight, repeated every four to six hours, as the symptoms require, in conjunction with the oral administration of the salt.

**Cardiovascular Complications.**—Cardiovascular disorders in scarlet fever consist of *bacterial endocarditis* due to bacteremia, and *streptococcal pericarditis*, and *endocarditis* and *pericarditis* of latent rheumatic fever origin. An endocarditis

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## SCARLET FEVER THERAPY (Continued)

Streptococcal Pericarditis	Sulfanilamide. Tapping if necessary.
Rheumatic Endocarditis Rheumatic Polyarthritits	Salicylates. Digitalis for congestive failure.
Benign Cardiac Murmurs	Bed rest only.

## SULFANILAMIDE DOSAGE

Weight of Patient	Routine Daily Dosage 1st-4th Day of Disease	Routine Daily Dosage 4th-8th Day of Disease	Routine Daily Dosage 8th-19th Day of Disease
25 lbs.....	40 grains	25 grains	15 grains
50 lbs.....	60 grains	35 grains	20 grains
100 lbs. and over.....	90-120 grains	60 grains	20 grains

Daily dose is divided into doses given at 4- or 6-hour intervals. Actual dosage depends on drug level obtained after 48 hours which should be at least 4 mg. per cent. In the presence of local infections a level of 6 to 8 mg. is desirable; in bacteremia and meningitis 10 to 16 mg. is desirable.

of rheumatic fever origin is the most common of these, but altogether these occur in only 0.5 per cent of the cases of scarlet fever.<sup>13</sup> Bacterial endocarditis and streptococcal pericarditis require drastic sulfanilamide therapy along with immunotransfusion. Tapping the pericardium may be necessary. The evidences of rheumatic fever, including polyarthritits, require intensive salicylate therapy, and, in the presence of congestive failure, digitalis. Benign cardiac murmurs are very frequent, especially during convalescence. If there is no history of rheumatic fever in the family or in the patient, if the heart was entirely normal at the onset of the scarlet fever, and if the sedimentation rate is relatively low, the chances are that the murmur, even though suggestive of valvular disease, will be transient. These benign murmurs need no further treatment than rest in bed.

## BIBLIOGRAPHY

1. Hoyne, A. L. and Welford, N. T.: Diphtheritic Myocarditis: Review of Four Hundred and Ninety-six Cases. *J. Pediat.*, 5: 642-653, 1934.
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Since this discussion today is concerned mainly with bacterial agents which cause purulent meningitis, the pathogenesis of tuberculous meningitis will not be discussed. It is fair to say, however, that tuberculous meningitis is rarely confused with other forms of bacterial meningitis, since it causes a lymphocytosis of the spinal fluid and not a purulent exudate.

TABLE 1  
RELATIVE FREQUENCY OF MENINGITIS ACCORDING TO CAUSATIVE AGENT

Organism	Neal <sup>1</sup>	Fothergill and Sweet <sup>2</sup>	Tripoli <sup>3</sup>	Rhoads et al. <sup>4</sup>	Total
Tubercle bacillus.....	1010	290	51	158	1509
Meningococcus.....	1566	160	221	105	2052
Pneumococcus.....	255	69	111	71	506
Streptococcus.....	274	69	24	36	403
Influenza bacillus.....	164	78	20	29	291
Miscellaneous.....	233	39	43	60	375
Total.....	3502	705	470	459	5136

The commonest cause of purulent meningitis is the meningococcus. The portal of entry is usually the nasopharynx, although the pathway from this region to the meninges is not always clearly defined.

The pneumococcus, hemolytic streptococcus and influenza bacillus share about equally in causing most of the other cases

TABLE 2  
DISTRIBUTION OF FATAL CASES OF MENINGITIS ACCORDING TO CAUSATIVE AGENT

Organism	No. of Cases
Tubercle bacillus.....	9
Meningococcus.....	12
Pneumococcus.....	13
Hemolytic streptococcus.....	18
Influenza bacillus.....	9
Miscellaneous.....	22
Total.....	83

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paranasal sinuses by physical means including x-rays for evidence of a local infection which might be a source of infection of the meninges.

### DIAGNOSIS OF MENINGITIS

The diagnosis of meningitis depends upon (1) the history, (2) the symptoms and signs of an infection, (3) the localizing signs of an infection of the meninges, and (4) the findings in the cerebrospinal fluid.

**The History.**—In any patient suspected of having meningitis the following points are significant: (1) previous or recent infections of the nose, throat, or ears, or recent operations in these regions, (2) previous or active signs of a pulmonary infection, (3) head injuries, and (4) a history of contact with patients who have meningococcal meningitis.

**Symptoms and Signs of Infection.**—There is nothing distinctive about the general signs of infection in cases of meningitis. The onset with *fever, headache, nausea and vomiting, pain in the back, and prostration* is common but not diagnostic of meningitis. The association of these signs with *stupor, convulsions, or coma* is, however, suggestive of meningitis especially when accompanied by either the signs of a focus of infection which might serve as a source of infection for the meninges, or the signs of increased intracranial pressure. Also the occurrence of *herpes* and a *hemorrhagic skin eruption*, and an associated *conjunctivitis* are suggestive of a possible infection of the meninges (meningococcal or influenzal infection).

**Localizing Signs of Meningitis.**—The localizing signs of meningitis are those indicating (1) an increased intracranial pressure and (2) irritation of the meninges with reflex muscle spasm.

The important physical signs of *increased intracranial pressure* consist of headache, nausea and vomiting, and engorgement of the veins of the ocular fundi, with choking of the optic disks and occasionally convulsions.

The signs of *irritation of the meninges* are: (1) spasm of the neck muscles causing stiff neck, with retraction of the head; (2) spasm of the erector spinae muscles with retraction of the back muscles, with opisthotonos when it is extreme; and (3) spasm of the hamstring muscles causing a positive Kernig's sign.

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8. Paralysis of the seventh nerve and deafness suggest an infection in the posterior fossa.

9. Paralysis of the third, fourth and sixth nerves, edema of the eyes and exophthalmos following middle ear disease indicates a spread of the infection to the cavernous sinus.

10. Bacteremia associated with middle ear disease and signs of meningitis should suggest thrombophlebitis of the lateral sinuses or jugular bulb.

11. Aseptic meningitis associated with mastoiditis indicates an infection in the immediate neighborhood of the meninges, i.e., perisinous abscess, lateral sinus thrombosis, or a brain abscess.

*Localizing Signs Associated with Meningitis Suggesting the Primary Focus in the Paranasal Sinuses.*—Meningitis is seen most often following infections of the frontal, ethmoid and sphenoid sinuses and, in a number of instances, there are associated signs of thrombosis of the cavernous sinus or paralysis of the cranial nerves which extend along the base of the anterior third of the skull.

The following features are of significance and importance in the diagnosis of the source of meningeal infection in the paranasal sinuses:

1. Meningitis following frontal sinusitis is usually secondary to a subdural or brain abscess. It is commonly associated with osteomyelitis of the frontal bone or thrombosis of the superior longitudinal sinus.

2. Edema of the upper eyelid and tissues over the frontal sinus means osteothrombophlebitis of the underlying bone and, under these circumstances, osteomyelitis of the skull and an abscess of the frontal lobe should be suspected.

3. In any patient with an acute frontal sinusitis, the sudden onset of convulsions, hemiplegia and aphasia usually suggests the development of a subdural abscess with the thrombophlebitis of the superior longitudinal sinus or the superficial cerebral veins.

4. Meningitis following a head cold due to the pneumococcus (usually Type III) without signs of otitis media or mastoiditis is suggestive of suppuration of the sphenoid or ethmoid sinuses. There is usually bacteremia and pain over the top of the head.

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4. Meningitis following a head cold due to the pneumococcus (usually Type III) without signs of otitis media or mastoiditis is suggestive of suppuration of the sphenoid or ethmoid sinuses. There is usually bacteremia and pain over the top of the head.

In infected fluids the *sugar content* is reduced and as recovery takes place it gradually returns to normal.

The *dynamics* of the cerebrospinal fluid should be tested in order to determine the presence or absence of an occlusion of the lateral sinuses or the jugular veins.

*Blood Cultures.*—Cultures of the blood should be made in all cases, since the presence of bacteremia is of significance in both diagnosis and prognosis. These should be made before any treatment is begun. In meningococcal meningitis the incidence of bacteremia varies between 5 and 60 per cent during the first week of the illness. In influenza bacillus meningitis, at least 70 per cent show bacteremia and, in pneumococcal cases, at least 50 per cent. In hemolytic streptococcus meningitis the incidence of bacteremia is usually high when there is an associated lateral sinus thrombosis, which occurs in at least 50 per cent of cases. The following points are worth noting about bacteremia in these infections:

1. In any patient with Type III pneumococcus bacteremia and meningitis who shows no signs of otitis media or mastoiditis, an infection of the sphenoid sinus or endocardium should be suspected.

2. In a patient with hemolytic streptococcus bacteremia and meningitis one should also suspect an associated thrombosis of the lateral sinus or jugular bulb.

3. In all patients with meningitis and bacteremia, regardless of the type of organism, one should search constantly for evidence of infection in the joints, endocardium and other organs.

#### PROGNOSIS IN MENINGITIS

In assessing any form of treatment, it is absolutely essential that the physician should be familiar with the natural history of the disease and the factors which influence the outcome. A few of the more important factors in meningitis may be listed as follows:

1. The organism.
2. The focus of infection preceding the meningitis.
3. Age of the patient.
4. Bacteremia.
5. The presence of associated diseases.
6. Type of treatment.

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period when the disease is appearing sporadically. This is a universal experience and one that should be appreciated.

*Pathogenesis.*—Once the organisms gain access to the nasopharynx they may set up a *rhinopharyngitis* but more often they give rise to no trouble. In some, the carrier state is transitory and lasts only a few weeks. During this time the individual may develop antibodies to the organism he is carrying so that a *subclinical infection* may be said to be present. In others, however, the meningococci invade the meninges either by the blood stream or by direct invasion. *Bacteremia* can be detected in between 5 and 60 per cent of the cases of meningitis within the first week, and in a few cases *foci of infection* appear in other parts of the body such as the joints or endocardium.

#### MENINGOCOCCUS MENINGITIS

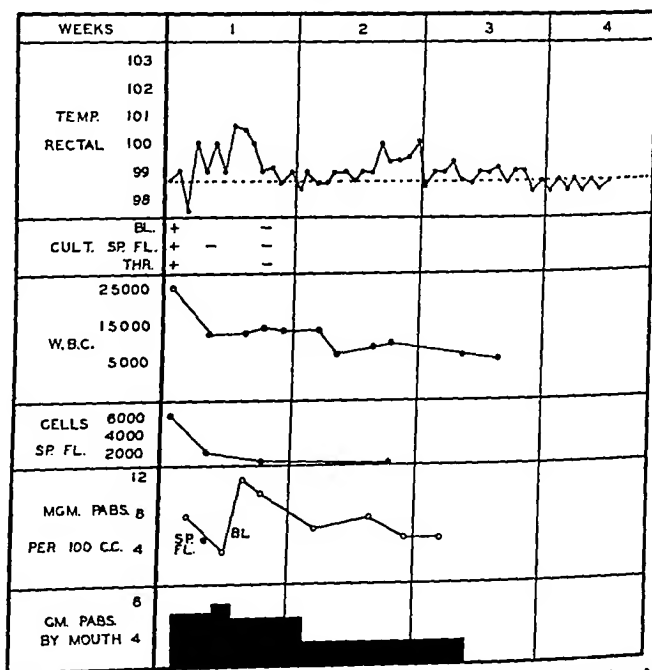


Fig. 172.—Clinical course of meningococcal meningitis with bacteremia in which sulfanilamide alone was given.

*Diagnosis.*—The diagnosis is established by means of lumbar puncture, but in all cases the blood and nasopharynx should be cultured for organisms. Although the presence of the clinical signs of meningitis, with extensive herpes labialis extending over the chin or neck, a hemorrhagic skin eruption, or hemat-





The fatality rate without treatment varies between 50 and 90 per cent, following serum treatment between 17 and 30 per cent, and following chemotherapy between 2 and 12 per cent.

The decrease in fatality rate has been attributed to (1) the introduction of chemotherapy, (2) fewer lumbar punctures, and (3) the prevention of extensive hemorrhages into the internal organs. There are undoubtedly other factors which are concerned with the outcome about which we know very little.

### Treatment of Meningococcal Meningitis

#### EXAMINATIONS TO BE MADE IN ALL CASES:

1. Blood culture.
2. Spinal fluid examination.
3. Examination of nose and throat for evidence of infection.

#### THERAPEUTIC PROCEDURES:

1. For adults, *sulfanilamide* or *sulfadiazine* by mouth, 8 gm. a day until the blood and spinal fluid are sterile. Then 6 gm. a day until all signs of meningitis have disappeared. For children, 4 gm. a day until all signs of meningitis have disappeared.

2. *Lumbar puncture* at the onset and then once daily until the fluid is sterile. If there are symptoms and signs of increased intracranial pressure, lumbar puncture should be repeated.

3. In children under five years of age, *antimeningococcus serum* should be given intravenously, 150 cc. by drip method, diluted with 150 cc. of 10 per cent dextrose and allowed to run in at a rate of between 30 and 60 drops per minute.

4. In adults with signs of *bacteremia*, serum should also be given intravenously if they fail to respond to chemotherapy within forty-eight hours.

5. If it becomes necessary to give *sulfanilamide* to *comatose* patients a nasal tube may be introduced into the stomach or the drug may be given by clysis in 0.8 per cent solution, or sodium sulfapyridine or *sodium sulfadiazine* can be given intravenously 5 to 8 gm. daily in two divided doses.

6. Recent reports from Scotland<sup>7</sup> indicate that *sulfathiazole* is as effective as the other sulfonamide drugs in the treatment of meningitis, even when the concentration of the drug in the cerebrospinal fluid does not go above 1.2 mg. per cent.

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The evidence, then, is suggestive that the age of the patient and the accessibility of the infections to surgical treatment are important factors in prognosis.

Following the use of chemotherapy the fatality rate has been reduced to between 20 and 40 per cent. Here again the most striking results have been obtained in patients over five years of age who have been treated with both drugs and surgical

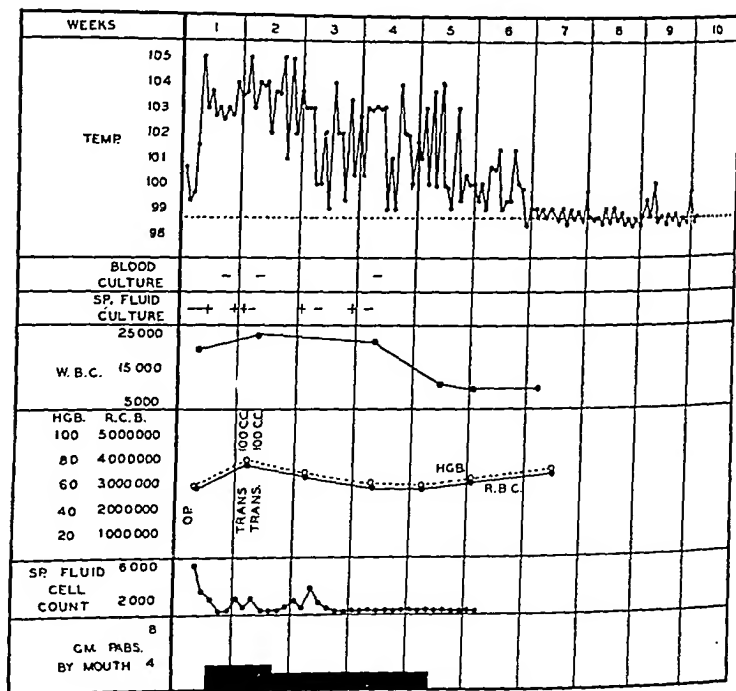


Fig. 173.—Clinical course of hemolytic streptococcus meningitis in a child following skull fracture.

drainage of foci of infection, although a definite improvement has been shown in patients under five years of age.

*Clinical Course.*—Figure 173 illustrates the course of events in a child with hemolytic streptococcus meningitis following a skull fracture. It is seen that it required at least six weeks for recovery to take place and three weeks for the spinal fluid to become sterile. Long-continued treatment is of the greatest importance in these cases of bacterial meningitis.

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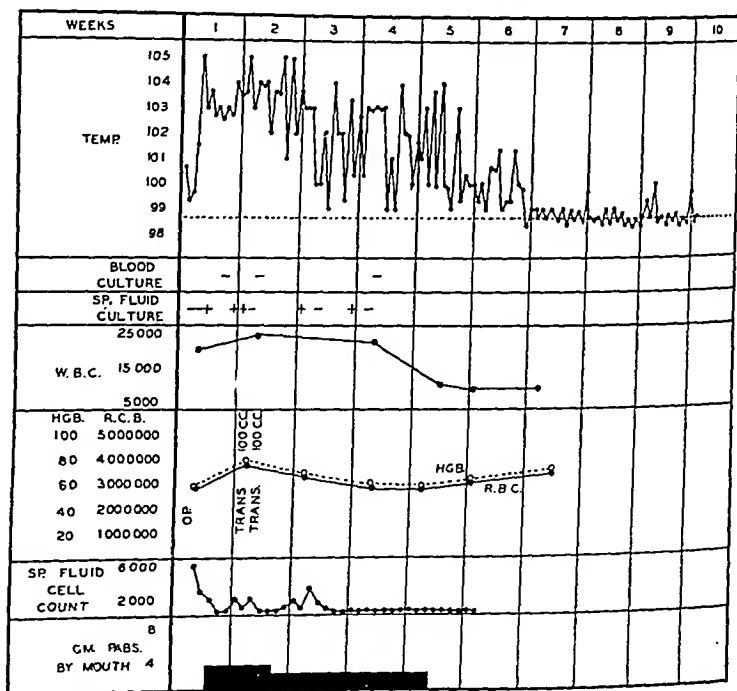


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*Type of Pneumococcus.*—When the meningitis complicates lobar pneumonia the types of pneumococci most frequently isolated are those which commonly cause pneumonia. They are also the types which commonly invade the blood. In order of frequency they are Types II, I, III, V, VII and VIII, and they are responsible for at least 75 per cent of all such cases. On the other hand, when the meningitis results from a focus of infection in the air passages or ears, then the common types are those which are usually found in the nose and throat. Type III accounts for at least 25 per cent of all such cases, whereas Types I, II, V, VII and VIII will account for another 30 per cent, and the remainder of the cases will be caused by the other types.

*Age Distribution.*—Pneumococcal meningitis has three peaks of incidence according to age; the first, under the age of two years, the second, between the ages of five and ten years when otitis media is common, and the third, between twenty and fifty years when pneumonia is most prevalent.

*Clinical Course.*—Since until recently most of the cases of pneumococcal meningitis were fatal, the illness was often of short duration and death followed within a few days of the onset of infection. Now that more patients are recovering, we are beginning to learn something about the course of the disease in those who recover. From the reported cases in which recovery has occurred and in the few cases which I have observed, the clinical course has been extremely variable. It has been found that the most favorable results have followed the combined use of specific serum and chemotherapy and in individuals who have meningitis which is unassociated with pneumonia or endocarditis. Unfavorable factors in prognosis appear to be the age of the patient, when it is under two and over forty years, and the presence of bacteremia, endocarditis, or debilitating diseases (cirrhosis of liver).

The *duration* of the infection of the meninges is extremely variable, so that it is not unusual to observe an infected cerebrospinal fluid for one to four weeks, with ultimate recovery of the patient. In the review of twenty-nine cases by Coleman<sup>14</sup> which included two cases of his own, the cerebrospinal fluid was sterilized in four days or less and the temperature returned to normal within one to seven days. On the other hand, in the

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cloudiness of the pneumatic cells of the right mastoid process and beginning cell destruction, a right mastoidectomy was performed. At the time of operation no active process was found and cultures from the mastoid were sterile. The meningitis became less acute but the patient continued to show a moderate increase in the cells of the spinal fluid for at least four weeks, when chemotherapy was discontinued. He continued to improve for three weeks when he had a relapse of his meningitis with bacteremia. On this occasion he was treated with sulfapyridine alone, but it will be noted from the chart that the spinal fluid contained organisms on various occasions for a period of four weeks. Finally, because he was complaining of nausea and vomiting, the sulfapyridine was discontinued and sulfadiazine was substituted.

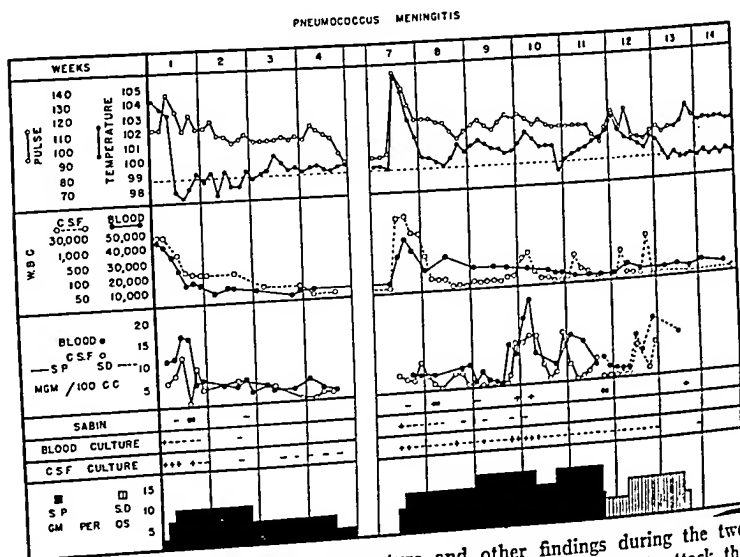


Fig. 174.—Course of the temperature and other findings during the two episodes of pneumococcus Type III meningitis. During the first attack the patient received serum as well as sulfapyridine. Note that the spinal fluid was more difficult to sterilize during the second attack than during the first and that it was more difficult to maintain high concentrations of the drug in the blood and cerebrospinal fluid.

Since the mastoid seemed to be excluded as a source for the recurrent infection, and since the left eye was the original site of the infection, it was deemed advisable to eviscerate the left eye in order to be certain that no source of infection was being overlooked. We were also influenced in this decision by the fact that he had already lost all useful vision of the eye. Following the evisceration of the left eye there was a reinfection of the spinal fluid for a day and then it became sterile again. Histological examination of the eye and culture of its contents failed to show any evidence of a chronic infection. Finally after fourteen weeks, during which time he was recovering satisfactorily, he began having muscular twitchings and spasm of the abdominal muscles. The spinal fluid was now sterile but it contained between 420 and

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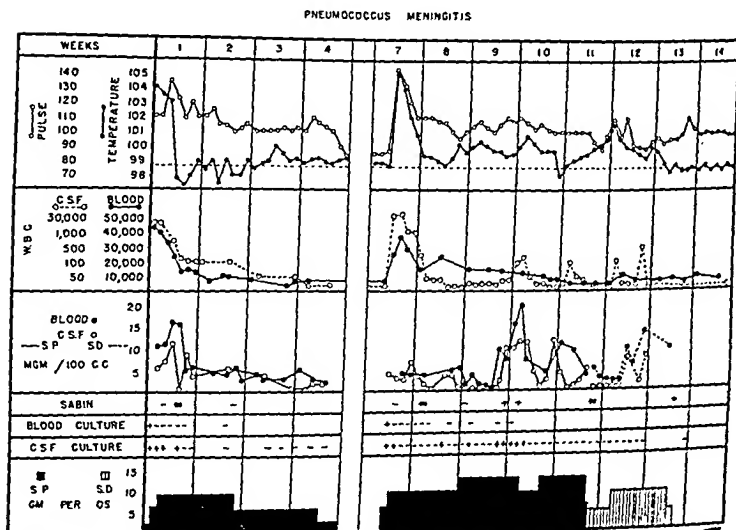


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5. The best method of treatment at present is a combination of serum intravenously and sulfapyridine by mouth, together with the surgical drainage of any focus of infection.

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7. Bacteremia occurs in at least 50 per cent of cases.

8. Relapses are common and may occur over a period of several months. They are probably due to either local areas of suppuration in the meninges or elsewhere which have not been drained, a complicating brain abscess, or a reinfection with a different type of pneumococcus.

### Summary of the Treatment of Pneumococcal Meningitis

#### DIAGNOSTIC PROCEDURES ON ALL PATIENTS:

1. Blood culture.
2. Spinal fluid culture with the identification of the type of organism.
3. Examination of the ears, mastoid and sinuses for foci of infection.

#### THERAPEUTIC PROCEDURES:

1. Type-specific *antipneumococcus rabbit serum*, 250,000 units, until a positive balance of antibody is obtained (positive Sabin or Neufeld test on patient's serum).

2. *Sulfapyridine* or *sulfadiazine* by mouth, 8 gm. a day. Maintain the cerebrospinal fluid level at at least 8 mg. per 100 cc.

3. *Lumbar puncture* at least once a day or oftener if signs of pressure develop.

4. *Sulfapyridine sodium*, 5 to 8 gm. a day, should be given intravenously if the patient is stuporous and cannot take the drug by mouth.

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children between the ages of two months and three years has no bactericidal power against *Hemophilus influenzae* Type B. After three years the bactericidal power gradually rises and appears to be permanent in adult life. It is not unlikely that the infrequency of influenzal meningitis in adults and its better prognosis is due to the presence of antibody at this age period.

*Prognosis.*—In the cases which are not treated with serum or with the sulfonamide drugs, the fatality rate varies between 98 and 100 per cent. In 1934, Neal, Jackson and Appelbaum<sup>21</sup> reported 111 cases with four recoveries following the use of anti-influenza serum, and they collected thirty-five cases, including their own, in which recovery had been reported. In analyzing the thirty cases in which recovery followed without serum it is seen that only eleven of the thirty patients were three years of age or under, showing that of the few recovered cases, 64 per cent were over three years of age. Since between 60 and 85 per cent of all cases occur under the age of three years, the age factor is important in assessing prognosis.

In a recent report by Neal, Appelbaum and Jackson<sup>12</sup> of twenty-nine cases of influenzal meningitis treated by means of serum and sulfapyridine, the fatality rate was recorded as 52 per cent. It was highest in patients with bacteremia and in those under three years of age. Thus, six of the eight patients with bacteremia died and all but two of those who recovered, *i.e.*, twelve of fourteen patients, had negative blood cultures. Ten of twelve patients under three years of age died and, of the fourteen who recovered, ten were over three years of age.

In a recent report by Alexander<sup>10</sup> the fatality rate was only 35 per cent in twenty-six cases in which treatment consisted of rabbit serum and/or sulfanilamide. These results are so impressive that a detailed analysis would seem to be in order. In fourteen of the seventeen cases with recovery on which there is complete information, seven or 50 per cent of the patients had bacteremia and eight were under three years of age. In the fatal cases, bacteremia was present in ten of the eleven cases and eight patients were under three years of age. Leukopenia was also a feature in four of the eleven fatal cases.

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it awoke crying as if it were in pain. This was soon followed by vomiting, diarrhea and fever; the temperature reached 104.8° F. by rectum, the vomiting stopped, and there was no further diarrhea. At this time it was noted that the child had a stiff neck but was able to move his arms and legs. These symptoms continued until he was admitted to the hospital.

Physical examination showed an infant with high fever, signs of bilateral otitis media, and stiffness of the neck. The red blood count was 3,200,000 and the white blood count 3600. Lumbar puncture showed a ground-glass fluid with 1600 cells, 96 per cent of which were polymorphonuclears. A smear showed a number of gram-negative, pleomorphic bacilli which were later identified as being due to *H. influenzae*.

The course of the illness is shown in the accompanying chart (Fig. 175).

#### H INFLUENZAE MENINGITIS

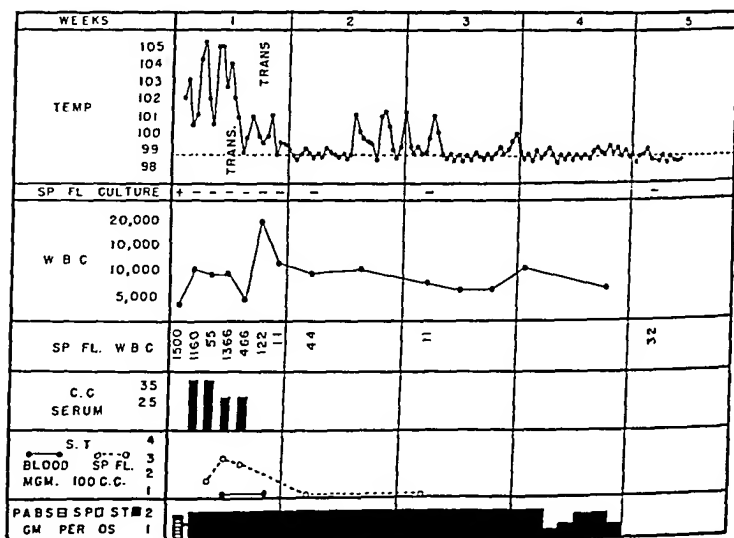


Fig. 175.—Clinical course of the illness in a case of *H. influenzae* meningitis, showing satisfactory response to serum and chemotherapy.

This infant responded very satisfactorily to serum and chemotherapy. The fluid was promptly sterilized, but the symptoms and signs of meningitis did not disappear for at least five weeks. The child recovered completely. Here again it is to be noted that the treatment had to be continued for at least four weeks.

A young boy, six and a half years of age, was admitted to the Massachusetts Memorial Hospitals in July, 1940, complaining of headache. Three days before entry he had some pain in the face which was thought to be due to toothache.

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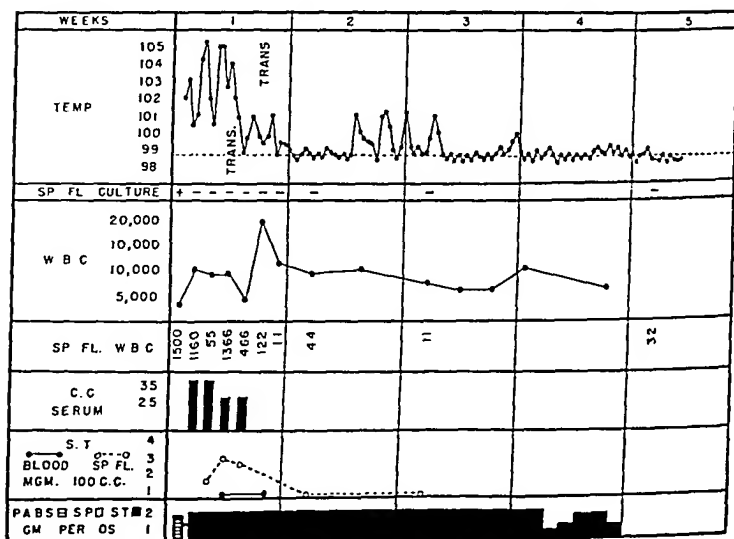


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A young boy, six and a half years of age, was admitted to the Massachusetts Memorial Hospitals in July, 1940, complaining of headache. Three days before entry he had some pain in the face which was thought to be due to toothache.

are likely to occur when the concentration of sulfapyridine in the spinal fluid decreases below 5 mg. per 100 cc. This boy finally recovered completely.

### Summary of Treatment of Influenza Bacillus Meningitis

#### DIAGNOSTIC PROCEDURES:

1. Blood culture.
2. Spinal fluid culture and smears.
3. Lumbar puncture at least every twenty-four hours.

#### THERAPEUTIC PROCEDURES:

1. Specific *antisera* (rabbit) until the blood is cleared and there is a positive balance of antibody in the circulating blood. Usually at least 100 mg. of antibody nitrogen are required for the initial dose.

2. *Sulfapyridine* by mouth so that the level is at least 8 mg. per 100 cc. in the spinal fluid, i.e., 2 gm. a day for small children, 4 gm. a day for older children. This should be continued until the spinal fluid is sterile.

3. The maintenance of *good nutrition* and the *prevention of anemia* are important.

The treatment recommended by Alexander<sup>16</sup> for infants and children may be summarized as follows:

1. One-tenth gm. of *sulfanilamide* per kilogram of body weight is given by intravenous drip as soon as the diagnosis is made. This is followed by 0.1 gm. per kilogram in 40 cc. of Ringer's solution every four hours.

2. *Fluids* are forced for at least three hours before serum is administered.

3. Twenty-five mg. of *antibody nitrogen* are given intravenously and 75 mg. are diluted in 200 to 300 cc. of Ringer's solution and given by intravenous drip over a two-hour period.

4. *Lumbar puncture* is performed daily and serum is discontinued if the spinal fluid is sterile, the sugar and chlorides are rising, the protein and cell count are falling and the concentration of 1:10 dilution of the patient's serum produces capsular swelling.

#### STAPHYLOCOCCAL MENINGITIS

There are now on record several cases in which the use of sulfathiazole or the other sulfonamide drugs has been followed

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## PATHOLOGY

**Mechanism of the Attack.**—Wolff and his associates,<sup>1</sup> in a series of brilliant experiments, have shown that the headache of migraine is due to *vasodilation* of certain branches of the external carotid artery. Such dilation occurs primarily in the extracranial branches, although the dural branches may also be implicated. There was no evidence that vasoconstriction of the internal or external carotid arterial trees plays any part in the production of cranial pain. Their experiments have shown that the scotomata, and probably the other pre-headache phenomena of migraine, are due to vasoconstriction of various branches of the internal carotid artery. "The essential migraine phenomena result from dysfunction of cranial arteries and represent contrasts in vascular mechanisms and vascular beds."<sup>1</sup> The *cause* of this "dysfunction" is as yet unknown.

**Etiology of the Disorder.**—Careful observation and questioning of large groups of *unselected* cases leads one inevitably to the conclusion that the primary etiologic factor in migraine is not the same in all patients. Any sizeable series of cases may be divided into groups showing predominant endocrine, allergic, psychogenic or other types of pathology. Favorable therapeutic results in these groups, obtained by rational but divergent methods, strengthens one's impression of a variable etiology. In addition, careful consideration of any single case reveals multiple contributory factors.

Until the migraine syndrome is broken down into its proper components, or is shown to be due to a common pathologic process, a working hypothesis may be formulated as a guide to adequate therapy: *Clinical and experimental evidence suggests that migraine is a symptom complex due to a cranial vascular dysfunction, in part dependent upon an hereditary tendency (probably in the nature of an autonomic lability), which is initiated by various pathologic processes, and complicated by the influence of multiple secondary abnormalities.* Thus the ideal treatment for migraine must be variable and individualized.

## DIAGNOSIS

**Characteristics of the Syndrome.**<sup>2</sup>—A family history of migraine is present in over 70 per cent. Allergic tendencies are frequent in the past and family histories. The majority who seek assistance are *women*. More than coincidental relationship with the menses is not as frequent as commonly believed. Many patients are repressed, idealistic perfectionists. *Emotional dis-*

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## SYMPTOMATIC THERAPY

**Ergotamine Tartrate.**—Ergotamine tartrate\* is reported to have been effective in approximately 90 per cent of 600 cases of migraine.<sup>8</sup> It is a specific means of aborting or terminating the migraine type of headache.<sup>9</sup> In a few cases it is reported to have exerted a preventive action. Relief is afforded by vasoconstriction of the branches of the external carotid artery.<sup>10</sup>

Many patients delay medication because they hope that the prodromata of a migraine attack will not culminate in headache. It cannot be overemphasized that early treatment is necessary in order to obtain the best results.

*Parenteral injections* are thoroughly effective in over 90 per cent of the cases.<sup>11</sup> Although intravenous injection affords rapid relief it should be used only under the direct and continuous supervision of a physician. No more than 0.25 mg. of ergotamine should be given at the first injection. This may be supplemented by a simultaneous subcutaneous injection of another 0.25 mg. Subcutaneous or intramuscular injection is most practical for routine use. The average effective dose is 0.5 mg. Results should be manifest within thirty to forty-five minutes. The patient may be instructed in self-administration of the drug, for which purpose the Busher automatic injector† is quite helpful. After ascertaining the effect of 0.5 mg. on several occasions, the drug should be progressively decreased to the minimal effect dosage.

*Oral administration* is effective in from 40 to 70 per cent of the cases.<sup>12</sup> Approximately ten times the parenteral dose is necessary in order to obtain sufficient absorption after ingestion. Thus the average oral dose is 5 mg. The entire five 1-mg. tablets should be broken and swallowed at one time. In cases wherein additional ergotamine is necessary, it may be ingested at the rate of 2 mg. per hour until a total of 9 to 11 mg. has been taken. If the tablets are crushed and allowed to dissolve beneath the tongue, their effect is more rapid and more complete than when ingested. Because of the taste of ergotamine, not many patients care for this form of therapy. Neither

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**Oxygen.**—Oxygen is useful in the abortion or termination of migraine. Alvarez reported that 88 per cent of ninety-seven cases with "typical migraine" headaches were relieved, although only 42 per cent were "completely" relieved.<sup>15</sup> The method is not specific for migraine. Oxygen may be of benefit when ergotamine fails. At times, oxygen and ergotamine are better than either alone. Oxygen combined with an analgesic will sometimes give relief in headaches otherwise unaffected by either method. It does not cause any accessory symptoms. It may relieve the gastric symptoms. Its administration is simple and without discomfort.

Oxygen may be administered by means of the *B.L.B. mask*, with appropriate adjustment of any standard inhalation apparatus, or by use of the ordinary basal metabolism apparatus. A delivery of approximately 100 per cent oxygen must be obtained at a flow of from 6 to 8 liters per minute. The flow is adequate if the rebreathing bag does not completely collapse at inspiration. Inhalation should be continued for at least two hours if adequate relief is not obtained sooner. Larger or repeated inhalations may be necessary in certain cases. Oral or rectal narcosis with 3 grains of nembutal is helpful in resistant cases. There are no contraindications to the use of oxygen as described.

**Miscellaneous Drugs.**—Other drugs are worthy of mention only as possible aids in occasional cases. Placebos are often as valuable as more "rational" means. Intravenous injections of 25 to 50 cc. of 25 to 50 per cent *glucose*, 20 cc. of 10 per cent *sodium chloride*, 1 gm. of *sodium thiosulfate* or 10 cc. of 10 per cent *calcium gluconate* have all been recommended as means of terminating an attack of migraine. The subcutaneous injection of  $\frac{3}{4}$  grain of *ephedrine sulfate*, 1 cc. of 1:1000 *adrenalin*,  $\frac{1}{2}$  cc. of 1:1000 *histamine* or 1 cc. of *antuitrin* is occasionally effective. Subcutaneous injection of 15 mg. of "Mecholin"\* is occasionally successful in cases wherein ergotamine has failed. Subcutaneous injection of from  $\frac{1}{100}$  to  $\frac{1}{50}$  grain of *atropine* is helpful in terminating the gastric components of an attack. Intramuscular injection of 120 to 180 mg. of *thiamin chloride* has recently been recommended. The inhalation of *amyl nitrite* is occasionally worth while.

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Specific treatment of "allergic migraine" consists primarily in avoidance of the offending allergen. In some instances, improvement is obtained by *desensitization* with autogenous vaccines or with extracts of the offending allergen. Nonspecific desensitization with *peptone* has met with success in some cases. *Ephedrine* or *adrenalin* is reported to relieve this type of migraine. In some cases the attacks are decreased in frequency and severity by the ingestion three times a day of from 5 to 15 grains of *calcium gluconate* and 5 drops of *viosterol*.

Desensitization with *histamine* has been successful in a few cases and warrants further investigation. Subcutaneous injections of 0.05 mg. of histamine are given twice a day for two days, increased to 0.066 mg. twice a day on the third day and gradually increased to 0.1 mg. twice a day by the fifth day. The injection of 0.1 mg. twice a day is continued for two to three weeks. "Desensitization" with oral *histaminase* has not yet been notably successful in migraine.

**Endocrine Therapy.**—Endocrine treatment of migraine seems justified in certain women because of a temporal relationship of the attacks to the menses, both in regard to onset and occurrence; abeyance of the attacks during pregnancy and lactation; and their disappearance after the menopause. On the other hand, a careful analysis of 163 *unselected* cases in women revealed that only 10 per cent were *definitely* related to the menstrual or ovarian cycles.<sup>18</sup> Another 22 per cent were questionably associated, and in the remainder the relationship was coincidental, or absent. Relief by *estrogenic therapy* was most significant in those with a definite relationship. After three years' treatment and observation, relief became progressively less noticeable. Certain cases even became worse after prolonged therapy. Nevertheless, in carefully selected cases estrogenic therapy may be of some value. There are no reliable reports as yet, concerning gonadogenic treatment in males.

*Emmenin*\* may be beneficial in women whose headaches are invariably associated with the menses, especially if the latter are scanty or delayed. Such patients are often small-boned and underweight. One teaspoonful or one tablet is given three

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Because only 58 per cent of the cases reported were relieved by ergotamine, some question exists as to diagnosis. It is possible that the sense of well-being due to an abundance of the B complex was underestimated in evaluating the results. It was reported that vitamin therapy was most effective in the preheadache phase and of very little value after the headache had developed. In many instances the usual migrainous prodromata fail to be followed by headache irrespective of the management of the case. Nevertheless, despite certain criticisms, the reported results warrant further investigation.

Treatment consists of the intramuscular injection of *thiamin chloride* in doses of 30 to 90 mg. daily for four weeks, followed by 30 mg. three times a week for two weeks, then 30 mg. once or twice a week for two or more months. The effect is enhanced by the oral administration of enough vitamin B complex to assure a daily intake of 2.25 mg. of thiamin, 2.5 mg. of riboflavin and 6 mg. of nicotinic acid. A reduction in the dietary carbohydrates is also advisable.

**Gastro-intestinal Therapy.**—This type of therapy for migraine has been largely disappointing. There is no acceptable evidence that any portion of the digestive system is specifically responsible for the attacks.

Gastric therapy in migraine is essentially the prevention of nausea and vomiting by atropine or oxygen during the attacks and the avoidance of indigestibles between attacks. Morlock and Alvarez in a review of 215 cases concluded "... that if disease of the liver and its ducts has any effect on migraine it is a beneficial one."<sup>20</sup> Clear-cut hepatic, cholecystic or duodenal pathology is infrequent in migraine. Gallbladder operations are tempting but the results are disappointing. Bile salts have been used with characteristic optimism and similar results. In a small group of carefully selected patients weekly *duodenal lavage* with 30 cc. of 33 per cent magnesium sulfate has been effective in about half of the patients. *Chondroitin-sulfuric acid* is supposed to supply the liver with detoxifying glucuronic acid in a utilizable form. Oral administration of 3 gm. per day is reported to have relieved from 60 to 70 per cent of fifty-eight patients.<sup>21</sup>

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Because only 58 per cent of the cases reported were relieved by ergotamine, some question exists as to diagnosis. It is possible that the sense of well-being due to an abundance of the B complex was underestimated in evaluating the results. It was reported that vitamin therapy was most effective in the preheadache phase and of very little value after the headache had developed. In many instances the usual migrainous prodromata fail to be followed by headache irrespective of the management of the case. Nevertheless, despite certain criticisms, the reported results warrant further investigation.

Treatment consists of the intramuscular injection of *thiamin chloride* in doses of 30 to 90 mg. daily for four weeks, followed by 30 mg. three times a week for two weeks, then 30 mg. once or twice a week for two or more months. The effect is enhanced by the oral administration of enough vitamin B complex to assure a daily intake of 2.25 mg. of thiamin, 2.5 mg. of riboflavin and 6 mg. of nicotinic acid. A reduction in the dietary carbohydrates is also advisable.

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can be established. Despite the frequent occurrence of ocular symptoms, evidence is lacking that the source of migraine lies in the visual apparatus. In most instances correction of ocular abnormalities is helpful but not curative. However, in one report of careful ocular examination of children with "headaches and migraine," 197 out of 200 patients were cured by correction of ocular defects.<sup>25</sup> Defects in refraction, accommodation and equilibrium should be corrected. Anisoconia should be investigated where apparatus is available.

**Psychotherapy.**—Psychologic methods of therapy in migraine are helpful in all instances. Many patients with migraine are ill adjusted, rigid, repressed perfectionists lacking the average "normal" outlets of emotional life. Added to this is the Damoclean threat of the attack itself. Superficial psychotherapy and adjustment in the field of mental hygiene add greatly to the total therapeutic effect in all cases. On the other hand, complete relief resulting from a purely psychotherapeutic approach is rare.

### SUMMARY AND CONCLUSIONS

Adequate treatment of migraine depends upon a carefully considered diagnosis and an understanding of the mechanism and cause of the disorder. Diagnosis is largely a matter of exclusion. The mechanism of the attack is common to all types. The fundamental cause is probably not the same in all cases. A detailed history is far more valuable than prolonged examination.

Symptomatic treatment is an attempt to counteract the common mechanism of the attacks. Ergotamine, ergonovine and oxygen are most successful in this respect. The use of non-specific analgesics is generally inadvisable, but occasionally they are necessary.

Preventive therapy must be diverse in order to correct the different abnormalities primarily responsible for the attacks. Different methods are indicated in various cases. None are successful in all instances.

Treatment of the patient as a whole is essential. All patients benefit from superficial psychotherapy. Many are improved by correction of contributory abnormalities.

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The frequency of grand mal attacks vary in individual patients from many a day to one in a year or two. Occasionally the attacks may be so frequent that the patient does not recover from one attack before another develops (status epilepticus).

*Jacksonian Epilepsy.*—The term "Jacksonian epilepsy" is used to describe attacks in which the convulsive movements start in isolated muscle groups, such as the fingers or toes on one side of the body and gradually spread to the neighboring muscles of that extremity, then to the trunk and the other extremity on the same time. Consciousness is usually preserved as long as the muscular twitchings remain confined to one extremity, but when the convulsive movements spread from one side of the body to the other, consciousness is lost and the attack assumes the nature of an ordinary grand mal. These localized, or Jacksonian, attacks usually indicate a focal lesion of the cerebral hemisphere of macroscopic or microscopic size and are commonly seen in patients with tumors of the brain or cortical scars secondary to trauma or vascular lesions.

*Petit Mal.*—This type of attack is the mildest of the epileptic seizures. It is most common in children where it may be the only manifestation of the epileptic state. Petit mal attacks in adults usually occur in individuals who are also subject to grand mal or psychomotor attacks. In a petit mal attack the patient usually stops what he is doing and stares blankly into space. Convulsive movements are usually limited to a few twitchings of the eyelids, facial muscles or upper extremities. These attacks are usually of short duration, lasting for only a few seconds but they may be more prolonged. Rarely there may be a transient loss of postural tone causing the patient to fall to the floor without any real loss of consciousness. In a few patients the petit mal attacks may be accompanied by a relaxation of the sphincters. The degree of loss of consciousness in attacks may vary from a complete amnesia for a period of a minute or more to only a brief period of a second or more of partial retardation of the activity of the higher cerebral centers which can be detected only by special methods. After a petit mal attack the patient is usually mentally alert and takes up with his activities at the point where they were interrupted by the attack. In children subject to petit mal the attacks are apt to be quite frequent, usually varying from six to 100 or more

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pathologic processes responsible for the seizure is much more difficult.

**History of the Patient.**—In the study of any given patient, a careful history should be taken of the circumstances accompanying the onset of the attack and an exact description of the sequence of events during and following the attack. The frequency of attacks without medication should be determined as well as the effect of various types of therapy. Family history should be inquired into with especial reference to convulsive seizures or any other neurologic abnormality in other members of the family. Careful attention should be paid to the birth and early developmental history, childhood infectious disease and head injuries which may have played a role in the onset of seizures.

**Clinical Study.**—In the clinical study of the patient there should be a careful physical and neurological examination, analysis of the urine, complete blood count, determination of the blood sugar and nonprotein nitrogen content, x-rays of the skull and lumbar puncture with measurement of the pressure and a chemical and serological analysis of the cerebrospinal fluid. In selected cases other tests may be indicated, such as a glucose tolerance test or a determination of the blood calcium content. Electroencephalography, while not absolutely necessary for the diagnosis, may give valuable information, and should be carried out if possible. Visualization of the ventricles and subarachnoid spaces by lumbar encephalography or ventriculography should be reserved for those cases in which the diagnosis of tumor cannot be excluded by other methods.

**Exclusion of Etiologic Factors.**—Careful study of the patient should exclude, as far as possible, all of the pathologic and physiologic abnormalities which may be accompanied by convulsive seizures. The most common of these are tumors, abscesses and other expanding lesions in the brain, infections of the central nervous system (syphilis, etc.) cerebral arteriosclerosis, uremia, cerebral vascular lesions, adenomas of the pancreas, parathyroid deficiency or other diseases of the nervous system or neighboring structures. In the vast majority of the patients no significant structural or physiologic abnormality can be found and in these patients the condition is spoken of as "idiopathic epilepsy." This term means only that we do

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be kept in school unless the frequency of the attacks unduly disturbs the routine of the classroom or unless mental deterioration requires special facilities. A long-continued schedule of psychotherapy may be of value in adjusting the patient to his difficulties, but it cannot be expected to have any significant effects on the frequency of attacks. Treatment of other members of the family is as important as treatment of the patient. Excess attention and oversolicitousness should be eliminated and the proper attitude toward the illness instilled in the parents and relatives.

Physical activity of the patient should be regulated so that he has a set time for eating and sleeping and for regular exercises each day. These exercises should be of a moderate nature. Participation in competitive sports is not to be encouraged. Meals should be of a wholesome and simple nature, with a proper amount of carbohydrates and proteins and an abundance of fresh fruits and vegetables. *Alcoholic beverages are to be absolutely avoided.* The bowels can be regulated by training and, if necessary, by the judicious use of mild laxatives. Enemas and drastic purges should not be needed. There should be eight to nine hours of sleep, with a set time for retiring and arising. The patient should not be allowed to stay in bed after the other members of the household have arisen. Special activities, such as parties, dances, movies, and so on should be encouraged. Swimming, horseback riding and other somewhat dangerous sports can be permitted when there are proper safeguards. The risk involved in such activities is justified in most instances in order to prevent the development of chronic invalidism. Activities which would endanger the lives of other individuals, such as the driving of automobiles, should be prohibited.

Commitment of the patient to an institution is not desirable unless mental deterioration or unduly violent or frequent attacks not controllable by treatment make it necessary. On the other hand, definitely deteriorated, destructive or dangerous patients should not be kept at home and allowed to ruin the lives of other members of the family.

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effective method of controlling this form of seizure. In children with petit mal or grand mal attacks, any of the above three drugs may be used and, in addition, the ketogenic diet is sometimes of value. The ketogenic diet is of no value in the treatment of seizures in adults.

*Withdrawal of Drug Therapy.*—When a given medical treatment has been effective in relieving the attacks it has been our experience that attempts to withdraw this therapy results in their almost immediate recurrence. This does not mean, however, that medicine must be given forever, but caution should be used in withdrawing the use of medicine. The sudden withdrawal of the effective medication may result in the precipitation of status epilepticus and the death of the patient. When the patient has gone two or more years without attacks the dosage of the medicine can gradually be reduced over a period of months and, if seizures do not recur, it can be entirely discontinued. In patients who have gone for several years without seizures, the electroencephalogram may be of value in determining whether a remission has been produced by these treatments (or has spontaneously developed) or whether the seizures are merely being held in check and continued treatment is necessary.

*Phenobarbital Therapy.*—Phenobarbital, 5-phenyl-5-ethyl-malonyl-urea, is marketed in the form of an elixir containing  $\frac{1}{4}$  grain in 1 dram (4 cc.) and in tablets of  $\frac{1}{4}$ ,  $\frac{1}{2}$  and  $1\frac{1}{2}$  grains. The  $\frac{1}{2}$ -grain and  $1\frac{1}{2}$ -grain tablets are usually scored to facilitate division. First used in the treatment of convulsive seizures by Hauptmann in 1912,<sup>4</sup> phenobarbital is also manufactured in this country and abroad under the trade names of *luminal* and *gardenal*.

*Dosage.*—In the treatment with phenobarbital a reservoir of the drug is established in the system and kept at a constant level by frequent administration. Since excretion is slow, this can be accomplished by administering the drug once or twice daily. The initial dose for an adult should be at least  $1\frac{1}{2}$  grains (0.1 gm.) daily, given in a single dose at bedtime or in divided doses of  $\frac{3}{4}$  grain (0.05 gm.) each. This dose should be increased to  $2\frac{1}{4}$  grains (0.15 gm.) daily ( $1\frac{1}{2}$  grains at bedtime and  $\frac{3}{4}$  grain at breakfast) if the smaller dose is ineffective. If attacks continue further, increases of  $\frac{3}{4}$  grain (0.05 gm.)

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over phenobarbital and the bromides in that it has very little or no hypnotic action, but regulation of the dosage is more difficult and minor toxic symptoms are more frequent. The drug is marketed in capsules of  $\frac{1}{2}$  grain (0.03 gm.) and  $1\frac{1}{2}$  grains (0.1 gm.).

*Dosage.*—The principle of the administration of dilantin sodium is similar to that of phenobarbital, that is, the establishment and maintenance of a reservoir of the drug sufficient to control the seizures. In the average adult the initial dose of the drug should be  $1\frac{1}{2}$  grains (0.1 gm.) three times daily. Owing to the alkalinity of the drug it is best given at meal times. If any seizures occur after two weeks of this dosage, it should be increased to 6 grains (0.4 gm.) daily, the extra dose being given at bedtime with a glass of milk or some food. Further increases in the dose should be by increments of  $1\frac{1}{2}$  grains (0.1 gm.) until the maximum dose of 9 grains (0.6 gm.) daily is reached. In the majority of adults 6 grains (0.4 gm.) is the optimum dose. In children over twelve or fourteen years the average dose is  $4\frac{1}{2}$  to 6 grains (0.3 to 0.4 gm.) and in younger children 3 to  $4\frac{1}{2}$  grains (0.2 to 0.3 gm.).

*Toxic Symptoms.*—The toxic symptoms<sup>a</sup> of dilantin sodium are similar to those of phenobarbital, except that nervousness or sleeplessness, rather than drowsiness, is more commonly an early symptom. Other toxic symptoms are gastric distress, nausea and vomiting, nystagmus, ataxia, dermatitis, gingivitis and psychotic symptoms.

The minor toxic symptoms, *nervousness* and slight unsteadiness or *ataxia*, are frequently transient symptoms in the first few days of therapy and disappear with continuation of the therapy, or when the dosage is temporarily reduced. *Nystagmus* and *ataxia* can be produced in practically all patients if the dosage is sufficiently high. A few adults will tolerate as much as 9 to 12 grains (0.6 to 0.8 gm.) but toxic symptoms usually develop when the dose is increased beyond  $7\frac{1}{2}$  grains (0.5 gm.). The appearance of these symptoms calls for a temporary or permanent reduction of the dosage. If the reduced dose is not effective in controlling the seizures and attempts to increase the dose again result in the appearance of toxic symptoms, a combination of dilantin sodium with phenobarbital or bromides should be tried.

*Gastric discomfort, nausea and vomiting* may be controlled by administering the drug along with a little bicarbonate of soda or with 15 minims of dilute hydrochloric acid. *Dermatitis* occurs in approximately 5 to 10 per cent of the patients and is usually of a scarlatiniform or morbilliform nature and is accompanied by fever. The rash usually disappears within a few days of withdrawal of the drug. Recurrence of the rash when treatment is reinstituted or the development of an exfoliative dermatitis precludes further use of the drug.

One of the troublesome toxic symptoms of the drug is hypertrophy of the gums, or *gingivitis*. This is most common in children and varies from a slight

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*Toxic Symptoms.*—The toxic symptoms<sup>8</sup> of dilantin sodium are similar to those of phenobarbital, except that nervousness or sleeplessness, rather than drowsiness, is more commonly an early symptom. Other toxic symptoms are gastric distress, nausea and vomiting, nystagmus, ataxia, dermatitis, gingivitis and psychotic symptoms.

The minor toxic symptoms, *nervousness* and slight unsteadiness or *ataxia*, are frequently transient symptoms in the first few days of therapy and disappear with continuation of the therapy, or when the dosage is temporarily reduced. *Nystagmus* and *ataxia* can be produced in practically all patients if the dosage is sufficiently high. A few adults will tolerate as much as 9 to 12 grains (0.6 to 0.8 gm.) but toxic symptoms usually develop when the dose is increased beyond  $7\frac{1}{2}$  grains (0.5 gm.). The appearance of these symptoms calls for a temporary or permanent reduction of the dosage. If the reduced dose is not effective in controlling the seizures and attempts to increase the dose again result in the appearance of toxic symptoms, a combination of dilantin sodium with phenobarbital or bromides should be tried.

*Gastric discomfort, nausea and vomiting* may be controlled by administering the drug along with a little bicarbonate of soda or with 15 minims of dilute hydrochloric acid. *Dermatitis* occurs in approximately 5 to 10 per cent of the patients and is usually of a scarlatiniform or morbilliform nature and is accompanied by fever. The rash usually disappears within a few days of withdrawal of the drug. Recurrence of the rash when treatment is reinstituted or the development of an exfoliative dermatitis precludes further use of the drug.

One of the troublesome toxic symptoms of the drug is hypertrophy of the gums, or *gingivitis*. This is most common in children and varies from a slight

seizures or when the effective dose of dilantin sodium produces toxic symptoms. The dosage of the combination must be worked out according to the needs and tolerance of the patient. Three to five doses per day of the combination of  $1\frac{1}{2}$  grains (0.1 gm.) of dilantin sodium with  $\frac{3}{4}$  grain (0.05 gm.) of phenobarbital or 15 grains (1 gm.) of sodium bromide are usually required in the more resistant cases.

**Ketogenic Diet.**—It has been shown that a shift in the acid-base balance of the body fluids to the acid tends to prevent seizures. This can be accomplished by the ingestion of acids or acid-forming salts, but the use of such substances for long periods is not desirable. A satisfactory acidosis which is better adapted to the physiology of the organism can be produced by a diet which contains such an excess of fats over carbohydrates that combustion of the fats is incomplete. Good results with this diet have been reported by Wilder,<sup>9</sup> Talbot,<sup>10</sup> and others.

The ketogenic diet is of chief value in the treatment of seizures *in children*. The diet can be continued for many months or several years without retarding the mental or physical development. The management of this diet is difficult and can be used in the home only when the parents are sufficiently intelligent to prepare the diet and the child cooperative enough to eat all of the food in the diet and to withstand temptation of sweets available outside of the home. The diet must be carefully calculated, all foods weighed or measured and the urine tested daily for the presence of ketone bodies in the urine. Superficial attempts to make the diet high in fats and low in carbohydrates are valueless.

The caloric intake should be calculated so as to maintain body weight and sustain growth. Twenty-five to 50 per cent should be added to the basal metabolic requirements according to the amount of activity. If basal metabolic tests are not possible, satisfactory results can be obtained by using 50 calories for each kilogram (2.2 pounds) of body weight. The diet should contain 1 to 1.5 gm. of protein per kilogram of body weight, and the fat and carbohydrate content calculated so that the number of grams of fat is two to four times that of protein plus carbohydrates, according to the degree of acidosis desired, or to the difficulty in establishing an acidosis as determined

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acidosis there is no improvement the diet should be discontinued. Any of the anticonvulsive drugs, phenobarbital, dilantin sodium or bromides, can be used in conjunction with the ketogenic diet if desired.

#### OTHER METHODS OF THERAPY

**Surgical Treatment of Convulsive Seizures.**—Whenever convulsive seizures are associated with surgically removable lesions of the brain, such as *tumors* and *abscesses*, removal of such lesions is indicated. It must be remembered, however, that relief from convulsive seizures will result in only about 50 per cent of cases of meningioma of the brain and in a much smaller percentage of cases of glioma or abscess of the brain.<sup>11</sup> In such cases further treatment with drugs is necessary.

In addition to the removal of expanding lesions, surgery has been advocated for the excision of *cortical scars*<sup>12</sup> secondary to cerebral trauma, vascular lesions and birth injuries on the assumption that such scars produce an irritation of the neighboring cortex and act as a trigger mechanism for the seizures. Good results of such excisions have been obtained by a few neurosurgeons. This treatment should be limited to the group of patients with focal attacks, which do not respond to medical therapy. In addition the excision of such lesions should be performed only by neurosurgeons who have the facilities for adequate localization of the lesion. Medical treatment should also be used in these patients after operation.

The excision of isolated *foci of abnormal electrical activity* as shown by the electroencephalogram is still in the experimental stage and is not to be advised as yet, since it is possible that the excision of such abnormal foci will only result in the shifting of the abnormality to another region of the cortex.

Operations other than on the central nervous system are not advisable unless they are indicated for reasons apart from the occurrence of convulsive seizures. Removal of the cervical sympathetics or portions of the large intestine, and operations on the sinuses, etc., have no effect on the ultimate course of the disease. Removal of tumors of the pancreas is, of course, necessary when the attacks are definitely proved to be related to hyperinsulinism. Removal of the carotid sinus may be of benefit in patients with carotid sinus syncope.

**Dehydration Therapy.**—It has been shown that excessive hydration tends to produce convulsive seizures, and dehydration has been recommended by Fay<sup>13</sup> as a method of treatment. For this therapy to be effective, the restriction of fluid intake must be great enough to produce a negative fluid balance. Such a negative balance cannot be maintained for very long without seriously interfering with the physiology of the body. The extreme degree of restriction in regard to the amount of fluids that can be taken and the dry nature of the foods allowed, make the application of this therapy impractical.

**Treatment of Patient During an Attack.**—Once an attack has developed there are no measures that will shorten its

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The most important *laboratory procedure* is the determination of the basal metabolic rate. A persistently elevated metabolism, in the presence of symptoms and signs, confirms the diagnosis of hyperthyroidism. The blood cholesterol is usually low in this disease, but it is not of diagnostic value. In doubtful cases the response to iodine, as gauged by the reduction in metabolism, is practically diagnostic.

#### TREATMENT

There are three main types of treatment: (1) *subtotal thyroidectomy* following adequate iodization, (2) *radiation*, and (3) *treatment by iodine alone*. I shall describe in detail the management of a patient with hyperthyroidism to be treated by thyroidectomy. The other methods of therapy and the management of complications will be illustrated by actual case reports.

**Preoperative and Postoperative Management.**—The patient is kept at rest in bed and iodine is administered as soon as the basal metabolic level is obtained. We usually use saturated solution of potassium iodide, 5 minims once or twice a day. The diet is high in calories, high in vitamins and contains extra amounts of fresh fruits, green vegetables, butter, cream and liver. The vitamin intake is supplemented by two yeast tablets ( $7\frac{1}{2}$  grains each) three times a day because of the great need for vitamin B in this disease. Sedatives such as phenobarbital,  $\frac{1}{2}$  to 1 grain three times a day, may be used freely. Chloral hydrate and morphine derivatives in the usual dosage are also useful. Digitalis should be used only in gross congestive failure or in rapid fibrillation.

On this regimen the patient improves subjectively, gains weight and his basal metabolic rate becomes lower. When this rate reaches a low level (in ten days to two weeks) the patient is considered ready for operation. Patients who are severely toxic or are otherwise poor risks receive 1000 to 1500 cc. of

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with removal of 20 gm. of tissue. She was discharged eleven days after operation in excellent condition, with a metabolic rate of  $-1$  per cent and pulse of 66.

The patient improved rapidly after the operation and was able to do housework. However, she began to feel the cold, perspired very little, became lethargic, had tinnitus and marked paresthesiae. On her first follow-up visit on January 17, 1939, the basal metabolic rate was  $-20$  per cent and the weight 134 pounds—a gain of 10 pounds. Examination showed coarse, cold, dry skin, slight puffiness of the face and lids, no evidence of exophthalmos or regrowth of goiter, and a slow heart rate.

For this postoperative low metabolic rate the patient received desiccated thyroid (U.S.P.),  $1\frac{1}{2}$  grains daily, over a period of six months. She felt much better soon after taking thyroid, i.e., she felt warmer, perspired more and had more energy. The basal metabolic rate ranged between  $-5$  and  $-11$  per cent. In February, 1941, after omission of thyroid for two months, the metabolic rate was again  $-21$  per cent and symptoms, previously associated with the low rate, returned. Consequently, desiccated thyroid, 2 grains daily, was resumed. She has felt well since then.

This patient had mild thyrotoxicosis relieved by thyroidectomy. She has developed a low basal metabolism, probably permanent in nature, which has responded adequately to desiccated thyroid.

**Case II.—Severe Thyrotoxicosis Contraindicating Prolonged Iodine Medication; Thyroidectomy; Postoperative Auricular Fibrillation.**—This patient, M. A. P., a fifty-seven-year-old housewife, entered the hospital on August 15, 1934, because of thyrotoxicosis of five years' duration. She had been taking iodine for eighteen months but was nevertheless very toxic. She had lost over 30 pounds in weight, and experienced considerable dyspnea and palpitation on exertion and slight swelling of the lower extremities. Examination showed undernourishment, hard irregular goiter, generalized arteriosclerosis, rapid pounding heart, blood pressure 170 systolic and 60 diastolic, and a few rales at the lung bases. Unusual findings were extreme tenderness of the costal margin, midthoracic kyphosis and barrel chest, all undoubtedly due to osteoporosis. The basal metabolic rate averaged  $+35$  per cent and the pulse 128 to 140.

With continuation of iodine and with rest the metabolic rate dropped to  $+38$  per cent, but there was no gain in weight. The patient was undoubtedly a poor risk because of the severity of the thyrotoxicosis, the duration of the illness and the cardiac complication. On September 4, a right hemithyroidectomy was done. On the following day she was very sick and developed auricular fibrillation, for which she received digitalis, 3 grains every four hours for five doses and  $1\frac{1}{2}$  grains daily thereafter. She improved rapidly after the first two days and the heart became regular on the third day. At discharge on September 13, the basal metabolic rate was  $+46$  per cent and the pulse 116.

The patient took 5 drops of potassium iodide solution and  $1\frac{1}{2}$  grains of digitalis daily for three months, felt much stronger and gained 15 pounds in weight. When she omitted medication, thyrotoxic symptoms recurred. She therefore returned to the hospital and underwent a left hemithyroidectomy on March 25, after adequate iodization. The reaction was mild and she was dis-

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levels on iodine, the patient is completely well and is working hard. On one occasion, when iodine was omitted, his basal metabolic rate rose to +18 per cent.

Hyperthyroidism places an excessive strain upon the patient with independent heart disease, as illustrated by the severity of cardiac symptoms in this case. Consequently, rapid alleviation of the thyrotoxicosis by surgery is indicated. If the patient is adequately prepared, thyroidectomy is relatively safe.

This case also illustrates that persistent hyperthyroidism may be controlled by iodine alone.

**Case IV.—Thyrotoxicosis Complicated by Diabetes; Thyroidectomy during Iodine Remission.**—M. H., a sixty-three-year-old widow, developed thyrotoxicosis and also polyuria and polydipsia following the death of her husband. A prominent lump had been present in her neck for about twenty-two years, following the last pregnancy, and this grew larger during the few months before admission on April 4, 1940.

Examination showed evidence of weight loss, hot, moist skin, slight exophthalmos, an irregular goiter which contained a single nodule, rapid heart, sclerotic vessels and a blood pressure of 164 systolic and 86 diastolic.

The urine showed a high specific gravity—1.035 to 1.040—and contained large amounts of sugar. The fasting blood sugar was 192 mg. per 100 cc., serum cholesterol 126 mg. per 100 cc. and the basal metabolic rate +39 per cent.

The following diagnoses were made: hyperthyroidism, diabetes mellitus and arteriosclerotic heart disease. Treatment consisted of the usual measures, a diet of 150 gm. carbohydrate, 80 gm. protein and 120 gm. fat, and sufficient insulin to control the glycosuria.

The patient improved rapidly. The glycosuria diminished considerably, the fasting blood sugar dropped to 143 mg. per 100 cc. and the daily requirement for insulin dropped from 30 units to 5 units as the basal metabolic rate declined to +5 per cent. On April 17 she underwent subtotal thyroidectomy under local anesthesia. On the first and second postoperative days there was slight ketonuria and the insulin requirement rose to 30 units a day. In general, the patient had very little reaction from the operation and was discharged April 26, 1940, on a diet of 120 gm. carbohydrate, 70 gm. protein and 110 gm. fat. The requirement for insulin was to be determined by her private physician. The metabolic rate on discharge was -10 per cent.

The patient maintained this diet and took insulin, 10 units daily, for ten days only and iodine for a month. The basal metabolic rate on iodine was -1 per cent; two months later, off iodine, it was -5 per cent. There was no evidence of thyroid regrowth, the blood pressure was 120 systolic and 70 diastolic, blood sugar 120 mg. per 100 cc. and the urine sugar-free.

This case illustrates the well-known fact that thyrotoxicosis increases the severity of coexisting diabetes and that relief of thyrotoxicosis makes the diabetes milder. It is therefore important to treat the former by the quickest method available, namely, subtotal thyroidectomy during an iodine remission.

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In this case, however, iodine seemed only to irritate the eyes. Also, neither thyroid nor a diuretic produced any immediate improvement. The ideal treatment in such a situation still remains to be discovered.

**Case VI.—Hyperthyroidism Complicated by Nutritional Deficiency State and Arteriosclerotic Heart Disease.**—L. J., a retired school teacher sixty-eight years old, entered the hospital January 26, 1938. His appetite had always been poor and he had ingested large amounts of alcohol over a long period of time. When he developed hyperthyroidism, he also developed evidence of nutritional deficiency. He had severe diarrhea and symptoms of cardiac failure. He showed marked wasting, fibrillary twitchings of muscles, pain and edema of both feet and legs, marked hyperesthesiae of feet, impairment of pain and vibration sense below the knees, active knee jerks and absent ankle jerks. The basal metabolic rate was +39 per cent. The electrocardiogram showed changes suggestive of myocardial damage.

In addition to the usual treatment, the patient received 6 mg. of vitamin B<sub>1</sub> daily, increased in a few days to 20 mg. daily. The improvement was gradual but definite. Pain and hyperesthesiae diminished and edema disappeared. The metabolic rate rose to +55 per cent, in spite of iodine, probably as a result of the improved nutritional state. Later the rate dropped to +34 per cent and the electrocardiogram showed normal conduction and return of normal T waves. His diarrhea persisted at the end of two weeks of treatment. However, with the administration of brewer's yeast powder, 1 dram three times a day and later 2 drams three times a day, the bowels became normal in about a week. After a right hemithyroidectomy his basal metabolic rate came down to +5 per cent, and he was discharged on March 4, 1938, on 5 drops of potassium iodide and 20 mg. of vitamin B<sub>1</sub> daily.

On this medication the patient improved considerably so that the second operation became unnecessary. His metabolic rate fluctuated between -5 and -16 per cent on iodine. By October, 1939, he had little evidence of neurologic disturbance. He felt well except for occasional attacks of angina.

This patient had hyperthyroidism and arteriosclerotic heart disease. Demands on the metabolism made by the overactive thyroid increased the severity of the existing malnutrition and precipitated latent beriberi and perhaps pellagra as well. One may conjecture as to how much of a role the deficiency state played in the cardiac picture. In such a case treatment must be directed to improve the nutritional state and correct the vitamin deficiencies before any attempt at operation is made.

It is interesting that hemithyroidectomy may reduce the severity of hyperthyroidism to the point where iodine alone can control the residuum.

**Case VII.—Exophthalmic Goiter with Vocal Cord Paresis; Stormy Postoperative Course; Complete Relief.**—E. P., a fifty-one-year old married chairworker, was admitted February 10, 1941, with a diagnosis of exoph-

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several years a new goiter developed and symptoms of thyrotoxicosis returned. The condition was complicated by a duodenal ulcer which had bled a year before and two months before. Following these episodes, the thyrotoxicosis increased in severity. The basal metabolic rate was +29 per cent, the vocal cords were normal and there was no evidence of tetany. The symptoms were mainly cardiac in nature and quite disabling.

The patient received the usual preoperative treatment with the exception that the diet was not only high in carbohydrates and in vitamins, but was also divided into six meals and bland in character. On iodine the basal metabolic rate dropped to -3 per cent in two weeks, and a subtotal thyroidectomy was done with removal of 35 gm. of hyperplastic tissue. She made an uneventful recovery and was discharged on January 13, 1941, nine days after operation.

When seen on March 5, 1941, the patient's basal metabolic rate was -21 percent (off iodine) and she had gained 14 pounds in weight. She was entirely well and the only remaining evidence of her disease was slight exophthalmos and puffiness of upper lids.

This case illustrates the fact that thyroidectomy is often necessary to relieve persistent hyperthyroidism, particularly if the disease has been present for a long time or has produced disabling symptoms as in this case. The presence of the complication of bleeding from a duodenal ulcer suggests that the thyrotoxicosis is having an unfavorable effect on the ulcer and argues for immediate relief.

**Case IX.—Colloid Goiter in Young Girl; Therapeutic Test with Iodine; Late Operation for Hyperthyroidism Followed by Myxedema.**—R. C., a female, was first seen on August 5, 1927, at the age of six years, and a diagnosis of colloid goiter was made. However, her basal metabolic rate of +55 per cent dropped to +17 per cent when Lugol's solution was administered, rose again to +68 per cent on omission of Lugol's solution and responded again to zero when it was resumed. The patient's condition, without any treatment, was observed for several years. The goiter increased in size and by January, 1932, it was clear that she had hyperthyroidism of a mild sort. Subtotal thyroidectomy was done November 9, 1934, at the age of thirteen, with removal of 135 gm. of hyperplastic tissue.

A month after operation the patient had a metabolic rate of -29 per cent and symptoms and signs of myxedema, namely, drowsiness, easy fatigability, slow activity, hoarseness, cold dry skin, puffiness of the face, large tongue and slow heart rate. On desiccated thyroid,  $\frac{1}{2}$  grain daily by mouth, she improved rapidly, evidence of myxedema disappeared and the basal metabolic rate rose to -9 per cent in a month. The daily dosage of thyroid was raised to  $1\frac{1}{2}$  grains over a period of two and one-half years and so maintained until January 7, 1941, when it was omitted. Symptoms and signs of myxedema soon returned and the metabolic rate dropped from -7 per cent, on omission of thyroid, to -30 per cent at the end of three months. Thyroid medication,  $1\frac{1}{2}$  grains daily, was therefore resumed and she has again responded to it in a satisfactory manner. Her last basal metabolic rate was -4 per cent.

During this period of thyroid substitution the patient has matured normally and maintained a normal rate of growth.

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ment because the inferior thyroid arteries are the main blood supply to the parathyroid glands. Not infrequently tetany is a transient manifestation following thyroidectomy, but at times, as in this case, it is permanent.

*Treatment of Acute Tetany.*—Acute tetany of severe degree gives alarming symptoms and may cause death. Consequently, treatment must be vigorous. Intravenous *calcium chloride*, 10 cc. of a 20 per cent solution, repeated in an hour, will give immediate relief. *Parathyroid extract*, 10 to 15 units daily, may be given for a few days to control an acute situation. It cannot be used for long because it rapidly loses its effect.

*Treatment of Chronic Tetany.*—The chronic state of tetany requires constant treatment. Several methods of treatment are available, and a given case may require one or all methods.

1. *High calcium, low phosphate diet* and additions of *calcium salts*. A low phosphate diet is attained by omitting milk, nuts, chocolate, bran, cheese and cocoa.

2. *Desiccated thyroid* to mobilize stored calcium in the body. Mild degrees of hyperthyroidism may accomplish the same thing. It helped in this case.

3. *Ammonium chloride*, 10 grains three or four times a day, to produce mild acidosis and thus mobilize calcium.

4. *Dihydrotachysterol* (A.T.10) by mouth. The dosage has to be regulated carefully by repeated blood calcium determinations, because dihydrotachysterol has marked cumulative effect. It is usually given in dosage of 3 cc. daily for five days and  $\frac{1}{2}$  to 1 cc. daily thereafter.

5. *Vitamin D* as fish liver oil or as viosterol,  $1\frac{1}{2}$  to 3 cc. daily, or as vitamin D<sub>2</sub>, 25,000 to 50,000 units daily.

**Case XI.—Recurrent Hyperthyroidism Responding to Irradiation.**—A. M., a twenty-year-old single woman, was admitted February 18, 1929, with a diagnosis of exophthalmic goiter. She responded to iodine and was completely relieved by thyroidectomy.

She remained well for the next eleven years. Following her marriage in February, 1940, she had a series of emotional upsets incidental to quarrels with her mother-in-law and unemployment on the part of her husband. By November, 1940, she had all the signs and symptoms of hyperthyroidism and a basal metabolic rate of +30 per cent.

Since recurrent hyperthyroidism seem to respond well to irradiation, it was decided to use this form of therapy rather than thyroidectomy. The patient therefore received 200 r daily for two days to the anterior surface of the thyroid, through a 10 by 10 cm. field with the larynx shielded, 200 K. V. and

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In addition, the patient presented several symptoms suggestive of hyperthyroidism, but no definite eye signs or goiter. Since these symptoms could also be due to the menopause, it was decided to treat the latter and leave the question of hyperthyroidism for the future. With intramuscular injections of estradiol benzoate, the menopausal symptoms improved considerably and the blood pressure dropped to 160 systolic and 80 diastolic. She was discharged May 11, 1940.

In spite of improvement in menopausal symptoms, the patient was not entirely well. There was persistent tachycardia, excessive perspiration, nervousness, and hot moist skin. The basal metabolic rate was +66 per cent. On iodine she improved promptly, gained weight and the metabolic rate dropped to +10 per cent. She has been maintained on iodine and has remained symptom-free. Her last basal metabolic rate on April 24, 1941, was -7 per cent.

This case represents the menopausal type of hyperthyroidism, which frequently responds to iodine alone. As the menopause subsides the hyperthyroidism may remit completely.

**Case XIV.—Mild Recurrent Graves' Disease Controlled by Iodine Alone.**—This girl, H. W., was first seen on April 20, 1934, when she was fifteen years old. She complained of prominence of the right eye, but had no other symptoms. She showed, in addition, bilateral goiter with bruit, rapid heart and fine tremor. The basal metabolic rate was +11 per cent and the pulse 100. On the basis of these objective findings, a tentative diagnosis of mild exophthalmic goiter was made and iodides were administered to confirm the diagnosis. The metabolic rate dropped to -12 per cent in a month, rose to +6 per cent when iodine was omitted and remitted spontaneously to -17 per cent in the course of five months without further treatment.

The patient was seen several times during 1935-1937, during which period she was symptom-free, had a small goiter and no eye signs, and the basal metabolic rate fluctuated between +1 and +10 per cent.

In the summer of 1939 the patient developed mild symptoms, prominent left eye, enlarged thyroid and basal metabolic rate of plus +14 per cent. On iodine she again improved and the metabolic rate dropped to +4 per cent in two weeks. She stopped iodine after a few weeks, but remained well. She had another relapse in February, 1941, and, as before, responded to iodine. She has remained well to date.

This case illustrates the chronicity of Graves' disease and its tendency to recur even after a seven-year course. This form of the disease is, as a rule, mild and may be controlled by iodine alone almost indefinitely.

#### CONCLUSION

The two greatest advances in the treatment of hyperthyroidism have been (1) the introduction and perfection of subtotal thyroidectomy by Kocher, Billroth and Halsted, and (2) Plummer's reintroduction of the use of iodine preoperatively

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stances make absolute confinement to bed impractical. The adoption of an ambulatory regimen does not mean, however, that the ideal of rest should be discarded. The physician, by becoming acquainted with his patient's daily activities, can often suggest periods of relaxation which are practical as well as beneficial. Arduous work may be temporarily lightened, regular and longer hours of sleep can be arranged, and week-ends can often be spent in bed. Each meal should be preceded and followed by a ten-minute period during which the patient does nothing but rest.

While at least some physical rest may be secured for every patient with peptic ulcer, the achievement of *mental rest* is much more difficult. Certainly nothing is accomplished by merely telling the patient "you must relax." Only after the physician has painstakingly ascertained his patient's emotional problems can he hope to give helpful advice. If the trouble is not specific but lies in the tense and expectant attitude with which the individual faces all his problems, much can be accomplished by teaching a *regularity of habits*. Regularity in sleeping, in working, in bowel habits and in eating is invaluable in alleviating what is known as "nervous tension." Above all, the physician must take care that no part of his treatment is so contrary to the patient's desires that the beneficial effect of the measure is entirely nullified by the emotional reactions evoked in the patient. Thus, in some individuals with mild symptoms, more relaxation may be secured by prescribing a vacation with moderate physical exercise than by enforcing rest. Fortunately these cases are in the minority; many patients with ulcer will make the necessary adjustments if the rationale and desirability of the disliked procedure are explained to them.

*Is Rest Effective in the Therapy of Ulcer?*—This question is best answered by presenting a short case report.

J. D., a white male of forty-three, entered the Massachusetts Memorial Hospitals with a story of intermittent ulcer symptoms over a period of ten years. He had never sought any medical advice for these, but entered the hospital because of a mild bleeding episode—his first. The treatment which consisted of rest in bed, a bland diet with interval feedings, and no alkalis completely relieved the patient of all symptoms. After three weeks, he was discharged with instructions to be up and about but not to work. Since mild symptoms recurred, he was given alternating antacids and milk-and-cream feedings every hour, a move which once more controlled his symptoms. One

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tracts having been shown to be more potent in this respect than alcohol. Fats are considered beneficial because of their demulcent action, and because they leave the stomach much more slowly than proteins and carbohydrates. That fats provide a strong stimulus for the secretion of the alkaline duodenal juices may be another point in their favor.

These principles of nutritiousness, blandness and mucosa-protecting action were incorporated in Sippy's milk-and-cream feedings, which still are the staples of most ulcer diets. During the first month of therapy, whether the patient is in bed or ambulatory, the diet should consist of the foods listed in Table 1.

TABLE 1

## FOODS TO BE TAKEN DURING THE FIRST MONTH OF TREATMENT

Milk		Cream soups (no meat broths, bouillon)
Cream		Meats (well-cooked and ground)
Eggs (soft- or hard-boiled, dropped)		Fish (not oily or fried)
Gelatin products		Chicken
Cooked cereals (cream of wheat, strained watery oatmeal)		White bread (toasted if desired)
Potato (mashed or baked)		Honey
Macaroni		Jelly
Spaghetti		Cream or cottage cheese
Peas	} pureed	Butter
Beets		Custards
Squash		Rice puddings (no raisins)
Spinach		
Carrots		

If therapy proves successful, the patient may eat the foods listed in Table 2, but these items should be added gradually and in small amounts so that three months elapse before the diet includes the entire list.

TABLE 2

## FOODS WHICH MAY BE ADDED AFTER THE FIRST MONTH OF TREATMENT

Meats (all kinds, except those which are very fibrous, tough, or spicy, such as poorer brands of pork, canned beef, sausage, ham)	Vegetables in Table 1 without pureeing
Potato (any form except fried)	Stewed fruit
String beans	Oranges, grapefruit (to be taken immediately after meals)
Asparagus	Ice cream
Cauliflower	Soft puddings
Lettuce (in small amounts, if well chewed)	Pies (apple or peach, if the crust is light)
	Coffee (only at meal times)

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cc.) should be taken daily, but, as in the case of hot or cold foods, not on the empty stomach.

*How Often Should the Ulcer Patient Take Food?*—It was Sippy's intention to neutralize the gastric juice by prescribing the frequent ingestion of food and alkali. Kirsner and Palmer,<sup>1</sup> however, have shown that milk and cream are rather ineffective as neutralizers. Yet dramatic clinical relief is often obtained by the milk-and-cream mixture, and peptic ulcers frequently heal rapidly on a rest and dietetic regimen alone. Hence, in the following feeding schedules, the primary purpose is *clinical relief*,

TABLE 4  
DOSAGE AND PROPERTIES OF SOME COMMON ANTACIDS

Antacid	Individual Dose	Favorable Properties	Unfavorable Properties
Sodium Bicarbonate	4 gm. 5i	Strong acid neutralization.	Liberates CO <sub>2</sub> in stomach. Causes "acid rebound." Most apt to cause alkalosis.
Calcium Carbonate or Magnesium Carbonate	2 gm. 5ss	Strong acid neutralization.	Liberates CO <sub>2</sub> in stomach. Causes some "acid rebound." Long use may cause alkalosis. Calc. Carb. constipates. Mag. Carb. is laxative.
Bismuth Subcarbonate	4 gm. 5i	Good demulcent. No "acid rebound."	Weak acid neutralizer. Constipates.
Magnesium Oxide	2 gm. 5ss	Strong acid neutralization.	Causes diarrhea. Some "acid rebound."
Aluminum Hydroxide	4-15 cc. 5i-5ss	Moderate acid neutralization. Good demulcent and astringent action. Little "acid rebound." No alkalosis.	Constipates. Expensive. May interfere with phosphate absorption.
Magnesium Trisilicate	2-4 gm. 5ss-5i	Moderate and slow acid neutralization. Long-continued action. No alkalosis.	On basis of clinical results, appears less effective than other preparations.

\* "Acid rebound" is the term applied to the increase in gastric secretion which follows the initial neutralization of the gastric juice by a strong antacid.

not acid neutralization. If no alkalies are ordered, the ambulatory patient is told to eat three moderate-sized meals a day, choosing his foods from those listed previously. One hour, and again two and a half hours after each meal, he may take one glass of a milk (2 parts) and cream (1 part) mixture (with or without a simple cracker), but the time spacing may have to be rearranged according to the symptoms. In doing this, the aim is prevention, not relief of symptoms. This means that the patient takes *three meals* and *six milk-cream feedings* per day. For the patient who is in bed, milk and cream is prescribed at

cc.) should be taken daily, but, as in the case of hot or cold foods, not on the empty stomach.

*How Often Should the Ulcer Patient Take Food?*—It was Sippy's intention to neutralize the gastric juice by prescribing the frequent ingestion of food and alkali. Kirsner and Palmer,<sup>1</sup> however, have shown that milk and cream are rather ineffective as neutralizers. Yet dramatic clinical relief is often obtained by the milk-and-cream mixture, and peptic ulcers frequently heal rapidly on a rest and dietetic regimen alone. Hence, in the following feeding schedules, the primary purpose is *clinical relief*,

TABLE 4  
DOSAGE AND PROPERTIES OF SOME COMMON ANTACIDS

Antacid	Individual Dose	Favorable Properties	Unfavorable Properties
Sodium Bicarbonate	4 gm. 5i	Strong acid neutralization.	Liberates CO <sub>2</sub> in stomach. Causes "acid rebound."* Most apt to cause alkalosis.
Calcium Carbonate or Magnesium Carbonate	2 gm. 5ss	Strong acid neutralization.	Liberates CO <sub>2</sub> in stomach. Causes some "acid rebound." Long use may cause alkalosis. Calc. Carb. constipates. Mag. Carb. is laxative.
Bismuth Subcarbonate	4 gm. 5i	Good demulcent. No "acid rebound."	Weak acid neutralizer. Constipates.
Magnesium Oxide	2 gm. 5ss	Strong acid neutralization.	Causes diarrhea. Some "acid rebound."
Aluminum Hydroxide	4-15 cc. 5i-3ss	Moderate acid neutralization. Good demulcent and astringent action. Little "acid rebound." No alkalosis.	Constipates. Expensive. May interfere with phosphate absorption.
Magnesium Trisilicate	2-4 gm. 5ss-5i	Moderate and slow acid neutralization. Long-continued action. No alkalosis.	On basis of clinical results, appears less effective than other preparations.

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strong neutralizers like calcium carbonate should be used. If antacids are to be given only three to six times a day, the slower but longer-acting aluminum hydroxide and magnesium trisilicate are recommended. In most ambulatory cases, the more infrequent dosage is effective and can be given one hour after food in place of the first interval feeding.

Under this plan, an average ambulatory patient might be treated as follows:

8:00 A.M.	.....	Breakfast (see diet list)
9:00	.....	Aluminum Hydroxide 8 cc. (3ii)
10:30	.....	Milk 120 cc. (3iv), cream 60 cc. (3ii)
12-1 P.M.	.....	Noon meal
2:00	.....	Aluminum Hydroxide 8 cc. (3ii)
3:30	.....	Milk and cream
5:30-6:30	.....	Evening meal
7:30	.....	Aluminum Hydroxide 8 cc. (3ii)
9:00	.....	Milk and cream
11:00	.....	Milk and cream

(before retiring)..... Aluminum Hydroxide 8 cc. (3ii)

*At night:* Every patient should have an antacid preparation at his bedside so that any nocturnal symptoms may be quickly alleviated.

This schedule, which is merely an example, must be arranged and adjusted according to the individual patient's (1) symptoms, (2) likes and dislikes, and (3) response to treatment. If symptoms occur within thirty minutes after meals, the time of the antacid or the feeding must be advanced; if symptoms occur regularly at night, the patient should be awakened about an hour previously to take both alkali and milk. Those patients who dislike the milk-cream mixture may use chocolate flavoring, or may take crackers, or may eliminate the cream entirely. If some clinical improvement is not noticed in three days, the diagnosis should be checked. When the treatment is ineffective in a patient with a proved duodenal ulcer, the therapeutic regimen must be altered: rest in bed, more frequent use of alkalies and feedings, and change of the antacid preparation, must all be considered in arriving at an effective therapeutic course.

**Laxatives.**—The diet and some of the antacids tend to cause constipation. This can be prevented by prescribing *mineral oil* or by using a *magnesium salt* in the antacid preparation. Mineral oil is less apt to leak if given in divided doses at meal times, such as 15 cc. (oz.  $\frac{1}{2}$ ) to 30 cc. (oz. 1) twice daily. In

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but none of the other belladonna side reactions (tachycardia, dry and flushed skin). Hence, 0.5 to 1.0 cc. (minims  $7\frac{1}{2}$  to 15) of the tincture is prescribed three times a day; and in order that the drug may be effective at the time when ulcer symptoms are most pronounced, it is given after meals. Belladonna may also be used in combination with sedatives and carminatives;

R	Tr. Belladonna .....	30.0 (5i)
	Sod. Brom. ....	30.0 (5i)
	Aq. Menth. Pip. ....	q.s. ad 180.0 (3vi)
Sig.:	4 cc. (5i) t.i.d. p.c.	

If the side reactions of atropine are too troublesome, the following *synthetic derivatives* may be used, but their advantages are not marked.

Novatropine—2.5 mg. (grain $\frac{1}{24}$ ) (Campbell products)
Sig.: 1-2 tablets t.i.d.
Syntropan—50 mg. (grain $\frac{5}{60}$ ) (Hoffman-LaRoche)
Sig.: 1 tablet t.i.d.
Trasentin—75 mg. (grains $1\frac{1}{4}$ ) (Ciba)
Sig.: 1 tablet t.i.d.

For severe pain, *nitroglycerin* 0.6 mg. (grain  $\frac{1}{100}$ ) under the tongue may be tried. *Benzedrine sulfate*, 5 mg. (grain  $\frac{1}{12}$ ) in the morning and repeated at noon, also may exert some antispastic influence, but its stimulating action on the central nervous system is of questionable benefit.

**Acid-Neutralization Therapy.**—If the aim of ulcer therapy is constant acid neutralization as Sippy's followers believe, the only completely effective method is Woldman's modification<sup>7</sup> of the *Winkelstein intragastric drip*. Aluminum hydroxide gel is diluted:

Aluminum hydroxide gel	1 part
Water	2 parts

and allowed to drip into the stomach day and night for ten days at a rate of about 15 drops per minute. The patient is kept in bed and is given a bland feeding every two hours. Since this regimen causes constipation, mineral oil daily or an enema every two days must be prescribed.

Since the diluted aluminum hydroxide gel is too viscous to run through a tube which is partially constricted by a clamp,

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together with thread. In order to eliminate sharp points, the distal free end is turned on itself and also tied with thread. The obturator is then placed inside the tube so that the tube's distal end overlaps that of the obturator by 1 inch. In passing the tube, its overlapping end is folded back. Since the obturator is left in the tube throughout the intragastric drip treatment, it must be securely fastened at the oral end of the tube.

If the patient refuses the indwelling nasal tube, the diluted aluminum hydroxide should be given every hour during the day and every two hours during the night. Kirsner<sup>2</sup> finds that effective neutralization is obtained by feeding milk-cream every hour and 2.0 gm. of magnesium or calcium carbonate every hour on the half hour. The undesirable feature of these oral regimens is that the patient must be awakened frequently at night if complete acid neutralization is to be attained. Nevertheless, patients with ulcers which do not respond to other therapeutic methods should be given a seven-day trial of the acid-neutralization technic, either by the drip or oral method. Attempts to control gastric acidity by intermittent drainage and lavage are probably not worth the trouble except insofar as they are used to determine the extent of acid-neutralization effected by any method. On the other hand, constant gastric suction-drainage combined with parenteral fluids, salts and glucose, occasionally relieves a markedly spastic and irritated duodenum if used for a period of two or three days.

**Mechanical Protection of Ulcers.**—*Gastric mucin* (Armour, Stearns, Wilson) has been prepared from hog stomachs and is used in 2.5 gm. (grains 40) doses every two hours in an attempt to coat the ulcer and thus allow it to heal. By itself, this treatment is not very effective, but if used in conjunction with the "basal treatment," it may help an occasional resistant case. The taste, however, is not very pleasant and should be disguised by mixing the mucin with other foods.

**Hormonal Therapy of Ulcer.**—Various neurohumoral mechanisms have been shown to exert some influence on the course of the human and experimental ulcer. Lesions at the base of the brain, especially those of the pituitary, favor the development of peptic ulceration, while pregnancy seems to alleviate this condition. *Urinary extracts* have been prepared which have an inhibitory effect on gastric motility and secretion. Metz and Lackey<sup>10</sup> believe that peptic ulcer is a manifestation of diabetes insipidus and have used *posterior pituitary*

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The *physical examination* reveals localized tenderness in the region of the gallbladder accompanied by a tender mass in about one third of the cases. In about 60 per cent of cases the patients have involuntary muscle spasm. Its absence in the remaining 40 per cent is probably due to a separation of the diseased organ and the parietal peritoneum by the liver.

**Treatment.**—Acute cholecystitis is a serious disease and the inflamed organ ultimately should be removed. However, cases behave somewhat differently, and there is a difference of opinion concerning the most desirable time for surgery. One group of practitioners holds that immediate surgery is always indicated, while a more conservative element has stressed the dangers of manipulating an acutely infected gallbladder and recommends a period of watchful waiting with the hope that the acute inflammation will quiet down. In any event, it is desirable for the internist who does not operate to call in the surgeon as soon as the diagnosis of acute cholecystitis is suspected. With our present knowledge the following routine of treatment, the object of which is to prepare the patient for operation, is the best course to pursue. During this period the physician may determine the direction which the disease is taking.

As soon as the diagnosis is suspected the patient is put to bed with the head of the bed raised from 6 to 12 inches. *Heat* or *cold*, whichever the patient finds more acceptable, is applied to the upper abdomen. Adequate *fluids* are given, the administration of which can be best assured by the intravenous route. Three thousand cc. of normal saline should be introduced during the first twenty-four hours. If the patient is very uncomfortable or unduly restless the use of *morphine* or *sedatives* is indicated. If the pain is severe, morphine sulfate 0.015 gm.

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### CHRONIC CHOLECYSTITIS WITH STONES

**Symptoms and Signs.**—This condition presents a different problem from that of the acutely inflamed gallbladder. In most patients the symptoms depend more upon the cholelithiasis than upon the cholecystitis, the severity of which varies greatly in different individuals. Cases present two different groups of symptoms and it is important to keep their differences in mind, particularly as they have a bearing on our attitude toward the character of treatment in chronic cholecystitis without stones.

1. The first group of symptoms consists of *discomfort in the right upper quadrant* which is *referred* characteristically to the back and to the region of the gallbladder. It may vary in intensity. Of patients with sufficiently severe symptoms to bring them to the operating table, approximately 90 per cent give a history of *biliary colic* or severe pain at some time during the course of their disease. Some patients describe a dull, heavy distress, while others refer to seizures with acute cramps or colic. The pain may last steadily for a matter of hours or it may be remittent, periodically becoming worse and better. In other cases it may be transient. The most typical point of reference is to the *tip of the scapula*, although the pain may go straight through to the back, to the interscapular area, or to the tip of the right shoulder. I saw one patient whose greatest complaint was hyperesthesia of both shoulders, so marked that the weight of his overcoat was distressing. At times the pain may be referred to the right lower quadrant and occasionally to the left side. Approximately two thirds of the patients experience pain in the right upper quadrant which is referred to the back. Approximately 10 per cent may complain at some time of pain in the left upper quadrant or left infrascapular region.

Approximately a third of all patients suffer from severe *epigastric distress*. *Vomiting* may occur spontaneously, but frequently it is induced by the patient in an attempt to overcome the associated nausea. Spontaneous vomiting is usually indicative of a stone in the cystic or common duct.

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bladder and because a certain number of patients lose these symptoms after a cholecystectomy, many normal gallbladders were operated upon.

*Cholecystograms* are a definite test of gallbladder function and the presence of stones. Intravenous cholecystograms are accurate in about 97 or 98 per cent of cases. Therefore, there is not the same need for relying upon symptoms as formerly.

**Treatment.—Surgery.**—Once the diagnosis of cholelithiasis has been made, cure can be effected only by surgery because, all the claims of patent medicine dispensers to the contrary, no method has yet been devised for the dissolution of gallstones. In spite of this knowledge, certain conservative clinicians do not advocate surgery for all patients. They point out that stones are found at autopsy in many cases in which no previous history of indigestion was obtained. Furthermore, it is well known that a patient may go many years before having a second attack of colic. Therefore, they argue, why subject a patient to an operation until it has been demonstrated that his gallstones are going to give him continuous trouble. Although there is much to be said for these arguments, careful statistics show that it is better to remove the stones provided the general condition of the patient does not contraindicate an operation. Whenever stones are present there is a potential danger of acute blockage of the cystic or common ducts which may be followed by the onset of a severe infection. Large stones may set up a chronic inflammation and may ultimately perforate unexpectedly. The mortality from an uncomplicated cholecystectomy has now decreased to a point where the danger of keeping the stones outweighs the danger of an operation.

It is a good rule, therefore, that gallstones should be removed surgically, particularly if the patient has suffered, or is suffering from acute attacks of biliary colic or chronic indigestion. One exception to this is the gallstone of an individual suffering from very definite complications which contraindicate the use of surgery—as, for example, active pulmonary tuberculosis. But it must be remembered that in most diseases the patient withstands the operation quite well. Another exception arises in the elderly person in whom the presence of stones produces little or no trouble. It may well be that such an individual may live the rest of his or her life without discomfort,

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diarrhea it should be stopped. Antispasmodics reduce the tone of the biliary tract. The inhalation of an *amyl nitrite pearl* or the use of *nitroglycerin*,  $\frac{1}{2}$  mg. ( $\frac{1}{120}$  grain), repeated if necessary two or three times, is sometimes helpful. However, if the pain is more severe an opiate, either *codeine sulfate*, 30 mg. ( $\frac{1}{2}$  grain) or *morphine sulfate*, 15 mg. ( $\frac{1}{4}$  grain), taken orally, will be needed.

#### CHRONIC CHOLECYSTITIS WITHOUT STONES

There is less agreement about the treatment of this condition, partly owing to a lack of unanimity concerning the definition and partly to uncertainty in the diagnosis. Various degrees of chronic inflammation of the gallbladder occur. On the one extreme is the thickened, shrunken organ about which there can be no question. At the other extreme are those conditions in which the gallbladder shows few or no gross changes and the microscope reveals only slight evidence of disease.

It seems to the writer that the subject of chronic cholecystitis today is in much the same state that chronic appendicitis was in a number of years ago. We have learned not to make a diagnosis of chronic appendicitis on vague symptoms and localized tenderness alone. The diagnosis of a pathologic appendix can only be made with reasonable assurance on the basis of three conditions: the history of characteristic symptoms, the presence of local signs and evidence of infection, *i.e.*, fever and leukocytosis. These three requirements hold equally true for chronic cholecystitis. As previously pointed out, pathologic gallbladders can cause functional symptoms from the gastrointestinal tract, but these symptoms are not diagnostic of a diseased gallbladder. They suggest merely that cholecystitis *may* be present. This is analogous to the difficulty in deciding whether the abdominal symptoms come from a low grade inflammation of the appendix or whether a functional disorder is simulating appendicitis.

Just as tenderness in the right lower quadrant does not alone make the diagnosis of appendicitis, tenderness in the right upper quadrant is not *always* the result of an inflamed gallbladder.

We have learned that minor histological changes can occur in the appendix without being evidence of clinical appendicitis. A similar situation exists in regard to the gallbladder.

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two or three teaspoonfuls of sodium phosphate in hot water before breakfast, or a moderate dose of magnesium sulfate, 2 teaspoonfuls before breakfast, will usually take care of bowel elimination in a satisfactory manner. The magnesium sulfate has the added value of tending to relax the sphincter of Oddi and, therefore, of assisting in overcoming biliary stasis.

In passing, a word should be said about the use of so-called *duodenal drainage*. When it was first discovered that it was practical to inject magnesium sulfate into the duodenum, with a resulting relaxation of the sphincter and a contraction of the gallbladder, this therapy seemed indicated. When it later became evident that fat was an even greater activator of the gallbladder it seemed hard to understand how this maneuver could be of value. In view of the observations which have been made through the ensuing years it seems probable that whatever beneficial effect this treatment has, can be attributed partly to the psychic effect and partly to its laxative action.

Irrespective of the basis underlying the medical therapy of gallbladder disease, it must be pointed out that it is very difficult to evaluate its results. The subsidence of true biliary symptoms after its use may only be coincidence, as it is well known that cholecystitis may become quiescent at any time. The improvement of nonspecific symptoms or the so-called "functional" symptoms may result from the regulation of diet and the better hygiene afforded the patient under treatment. It must always be kept in mind that antispasmodics may relieve purely gastro-intestinal symptoms. The only accurate way to determine the results of therapy is by observing what effect such treatment has on the x-ray appearance. As pointed out, this is, in itself, a difficult thing to evaluate and there have been too few reports, with the x-ray employed as a criterion of treatment from which to draw accurate conclusions.

From the foregoing it appears that the medical therapy which has been outlined for chronic cholecystitis is based on sound physiologic and pharmacologic considerations, but more careful and critical studies are needed to determine the clinical efficacy of this treatment. With our present knowledge, one is justified in making use of this procedure for patients with mild cholecystitis. Obviously it cannot correct a more advanced condition, for which one has to utilize surgery.

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especially since the methods of treatment are so successful. The first step in making the diagnosis is to suspect the disease. The diagnosis can then be established by the identification of the motile or cystic forms in the stool.<sup>6</sup> As a rule, patients with acute dysentery pass the motile forms; those with partial or well-formed stools pass cysts. The motile forms are easily recognizable on direct microscopic examination of a warm stool. The cysts require somewhat more experience to identify, and it is in such stools that special cultures are frequently of value. In addition, the complement fixation test as devised by Craig<sup>7</sup> is of some aid in establishing the diagnosis.

### TREATMENT

**General Measures.**—The general therapeutic aims in treating acute diarrhea of any cause are: (a) to quiet excessive peristalsis, (b) to relieve pain, and (c) to combat dehydration. Specific measures are directed toward the eradication of the infectious process.

**Antiperistaltic Measures.**—Fundamental in quieting excessive peristalsis are rest and warmth. The patient should be at bed rest, preferably in a hospital. If restlessness is marked, small doses of a sedative are indicated. Phenobarbital 0.03 gm. three times daily is usually sufficient.

**Control of Pain.**—In order to control the pain associated with the active peristalsis, it may be necessary to give opium. Paregoric in repeated doses of about 4 to 8 cc. every two hours until relief is obtained is most satisfactory. Large amounts of paregoric should not be used, since it may mask some of the toxic symptoms produced by the specific drugs.

**Fluids.**—In all patients, and especially in children, the maintenance of proper water balance is important. In general, some fluids can be given by mouth without producing nausea and vomiting; if necessary, additional fluids in the form of saline, or saline and 5 per cent glucose, should be administered either intravenously or subcutaneously. In adults the intake should exceed 3 liters. A good index of the degree of dehydration can be obtained not only from the clinical picture, but also from the specific gravity of the urine specimens. A specific gravity below 1.020 usually indicates adequate fluid intake.

**Diet.**—The diet should be nourishing and easily digestible.

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**Diet.**—The diet should be nourishing and easily digestible.

of serious damage. An example of one type of disabling reaction to emetine is given in the following case.

CASE I.—A twenty-five-year-old male entered the hospital immediately following the onset of a severe bloody diarrhea. Within eighteen hours active amebae were observed microscopically. Organisms were also cultured from the stools. Treatment was instituted at once; emetine hydrochloride in a dose of 0.03 gm. was given the first two days, followed by 0.06 gm. daily for nine days. In addition, emetine bismuth iodide was given orally in doses of 0.06 gm. each day. The diarrhea was checked within twenty-four hours. On the fourth day the patient complained of mild nausea which persisted for several days. At no time did vomiting occur. On the seventh day, the number of stools suddenly increased from one to three per day. Treatment was continued until the eleventh day. In all, 0.6 gm. of emetine and 0.6 gm. of emetine bismuth iodide had been given.

At the end of this period of therapy the patient complained of no symptoms. Several days later when he was allowed out of bed, muscle weakness was so severe that he was unable to walk more than a few yards. This generalized muscle weakness was incapacitating for over six weeks, and fatigue on exertion was present for another six months.

In summary, then, this patient's complaints were only mild *nausea* on the fourth day of treatment and a slight *diarrhea* on the seventh day. It was not until after discontinuance of therapy that severe muscle weakness became evident. The three most common early toxic symptoms are *nausea*, *vomiting* and *diarrhea*. Any sudden increase in the number of stools during the course of emetine therapy usually indicates toxicity. When such symptoms occur, emetine should be discontinued.

In general, emetine acts as a protoplasmic poison, with special predilection for cardiac muscle.<sup>9</sup> It is not uncommon to observe the development of arrhythmias during therapy. Muscle weakness, such as recorded above, and even muscular palsy may occur. Following large doses, death has been recorded. However, if the early toxic symptoms are kept in mind, emetine proves a very useful drug in the treatment of amebiasis.

Carbarsone.—This drug, introduced by Reed, Anderson, David and Leake,<sup>10</sup> has proved to be especially useful. Apparently it is the most effective arsenical preparation and, at the same time, the least toxic. It is administered orally in a dose of 0.25 gm. twice a day for a period of ten days. If the drug is given in larger amounts, or for a longer period of time, arsenical poisoning may result.

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every two days are administered simultaneously with the emetine treatment. Carbarsonne is most frequently used in mild cases of acute dysentery and in the chronic form of amebiasis. When this drug is used alone the infection is eliminated in about 90 per cent of the cases, but if at the same time yatren retention enemas are given as outlined above, about 97 per cent are cured.<sup>11</sup>

### BACILLARY DYSENTERY

Bacillary dysentery occurs sporadically throughout the United States and is endemic in many sections of the South. Lyon,<sup>12</sup> reporting from West Virginia, found that 37 per cent of 300 children observed over a five-year period developed dysentery. The majority of these cases were caused by the Flexner group of organisms. The disease is more likely to occur in rural areas although urban populations are in no way immune. Each year New York City reports several hundred cases of bacillary dysentery. The majority of infections occur in children; in adults they are somewhat more likely to go unrecognized.

### PATHOLOGY

The pathologic changes have recently been reviewed by Ch'in and Hu.<sup>13</sup> Briefly, it may be said that the first changes are congestion and swelling of the mucosa of the colon and/or the terminal ileum. This proceeds rapidly to ulceration, which is not infrequently covered by a thick, diphtheritic membrane. Gangrenous involvement is rare. Healing begins to take place at about the third week, although in some instances chronic changes ensue and the patient continues to excrete bacilli in the stool. In such instances the intestinal wall becomes thickened and granular. It is an interesting fact that the organisms rarely invade the blood stream, which is in striking contrast to typhoid infection. Secondary changes in other organs are observed especially in the kidneys, liver and central nervous system.

In the kidney the most constant change is degeneration of the cells of the collecting tubules producing a picture of nephrosis. The liver may show areas of fatty degeneration. The edema produced in the central nervous system is probably due to the elaboration of an exotoxin.

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*fluid balance* must be maintained. *Hospitalization* is indicated in the majority of cases, since the disease may be fulminating.

Fortunately, most cases recover without specific therapeutic measures. However, there are three types of infection where specific therapy is desirable. In the severe types of dysentery the mortality rate may be high,<sup>15</sup> and in such cases symptomatic therapy alone is of little avail. A few cases pass into a chronic phase and may continue to show organisms in the stools. The third type is the case which enters a long period of convalescence before return to normal health. Specific therapy in the last two types is certainly desirable.

*Serum and Vaccines.*—The use of serum and vaccines in the treatment of bacillary dysentery has been most disappointing. In acute cases the transfusion of blood obtained from recently recovered cases has been recommended. In chronic cases Felson<sup>16</sup> advises the use of a vaccine made from the infecting dysentery organism, enterococci and *B. coli*. Results from such therapy have not been too encouraging. When the dysentery is due to the Shiga type, antiserum may be of some benefit.

#### CHEMOTHERAPY

The use of *sulfanilamide* in the treatment of bacillary dysentery has been of little value.

**Sulfathiazole.**—When sulfathiazole was introduced, it soon became evident that this compound exhibited considerable bactericidal action against the organisms of the typhoid-dysentery group.<sup>17, 18</sup> The Flexner strains were found to be especially susceptible to sulfathiazole.<sup>18</sup> We have treated several cases with this drug. In one patient, who had positive cultures in both the urine and feces, a dramatic recovery and sterilization of the urine and feces followed sulfathiazole therapy. The number of cases treated with this drug has been too small to draw any conclusions as to its efficacy. If sulfathiazole is used, it should be given in doses of 1 gm. every four hours. In addition, the use of retention enemas of a saturated solution would appear justified, since little of the drug is absorbed when administered by rectum.

**Sulfaguanidine.**—More recently a new sulfonamide has been prepared.<sup>19</sup> This drug is especially interesting in that, although it is more soluble than sulfathiazole in water, it is ab-

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In chronic bacillary dysentery sulfaguanidine therapy may prove valuable. Figure 178 shows the course of illness in such a patient.

CASE II.—A twenty-year-old male student entered the Evans Memorial complaining of diarrhea of three months' duration. The onset of the illness was sudden and was not accompanied by symptoms other than diarrhea. He had from six to eight bowel movements daily. These stools were watery and contained considerable mucus but no blood was observed. The patient continued with his school work until a few days before admission when, because of weakness and loss of weight, he consulted his physician.  $\alpha$ -Rays of the colon at that time revealed a somewhat narrowed lumen and the mucosa appeared markedly irregular.

The patient's past history revealed the interesting fact that his family always used whole raw milk. At the age of fourteen he had an appendectomy, and at the age of seventeen his stomach was resected and a gastro-jejunostomy performed because of a peptic ulcer. Since that time he had no complaints other than hemorrhoids a year before entry.

On admission he appeared chronically ill. His skin and mucous membranes were pale. There were two abdominal scars, one in the right upper quadrant, the other in the right lower quadrant. No tenderness was noted on palpation and no masses were felt. The remainder of the physical examination was not remarkable.

Laboratory examinations revealed a leukocytosis of 12,000, hemoglobin of 57 per cent, and a red blood cell count of 4,180,000. The stools were soft, light in color, and contained considerable mucus. Occasionally gross blood was observed. Upon microscopic examination leukocytes were found to predominate but a few red cells were always present. No amebae were observed. Cultures revealed Flexner organisms on every occasion. The agglutinating titer against the patient's own organism reached 1:160.

In addition to the general supportive care, the patient received blood transfusions and sulfaguanidine. The drug was administered every six to eight hours, the total amount of drug given daily being indicated on the chart. Frequent determinations of sulfaguanidine were made on the stools and the blood. The concentration in the stools was always adequate and the levels in the blood were low. Except for a positive stool on the eighth day of therapy, daily cultures failed to reveal Flexner organisms after the third day. During therapy the cultures were made following a special technic which eliminated most of the drug. The stool was then added to culture media containing para-amino-benzoic acid.

In summary, then, this case represents an example of chronic Flexner dysentery in which the stools became negative following the administration of sulfaguanidine. The stools decreased only slightly in number and, although they became somewhat thicker in consistency, they still continued to show considerable numbers of leukocytes and red cells. It is likely that the intes-

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Laboratory examinations revealed a leukocytosis of 12,000, hemoglobin of 57 per cent, and a red blood cell count of 4,180,000. The stools were soft, light in color, and contained considerable mucus. Occasionally gross blood was observed. Upon microscopic examination leukocytes were found to predominate but a few red cells were always present. No amebae were observed. Cultures revealed Flexner organisms on every occasion. The agglutinating titer against the patient's own organism reached 1:160.

In addition to the general supportive care, the patient received blood transfusions and sulfaguanidine. The drug was administered every six to eight hours, the total amount of drug given daily being indicated on the chart. Frequent determinations of sulfaguanidine were made on the stools and the blood. The concentration in the stools was always adequate and the levels in the blood were low. Except for a positive stool on the eighth day of therapy, daily cultures failed to reveal Flexner organisms after the third day. During therapy the cultures were made following a special technic which eliminated most of the drug. The stool was then added to culture media containing para-amino-benzoic acid.

In summary, then, this case represents an example of chronic Flexner dysentery in which the stools became negative following the administration of sulfaguanidine. The stools decreased only slightly in number and, although they became somewhat thicker in consistency, they still continued to show considerable numbers of leukocytes and red cells. It is likely that the intes-

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The presence of normal *kidney function* may be established if a voided urine specimen shows a specific gravity of 1.026 or higher. It may be necessary to restrict the fluid intake for a period of twelve to eighteen hours to achieve this result. If nitrogen retention is suspected, it is wise to omit the concentration test and perform a *phenolsulfonphthalein test* by injecting intravenously 1 cc. of a solution containing 6 mg. of phenol red after the patient has first emptied his bladder and then ingested about 400 cc. of water. If the specimen voided fifteen minutes after the injection shows 20 to 30 per cent excretion of the dye, a concentration test may be safely attempted. If the urinary specific gravity is less than 1.026 and the fifteen minute excretion of phenolsulfonphthalein is less than 15 per cent, *impairment of renal function* exists. If under such conditions the blood nonprotein nitrogen is elevated, then *renal insufficiency* is present. At times, it may be necessary to catheterize the patient to secure a sterile specimen of urine for culture and examination of the sediment. To rule out congenital anomalies and long-standing infectious renal conditions, *intravenous pyelography* with diodrast should be done in certain cases. The appearance time and concentration of the diodrast in the kidney offer an excellent test of renal function. The correlation of the results of the complete history, physical examination, and laboratory studies enables the physician to determine the phase of the disease and its severity; the treatment to be undertaken then becomes evident.

#### STAGES OF THE DISEASE

##### A. *Acute Diffuse*

1. Silent (asymptomatic, insidious)
2. Overt (symptomatic)

##### *Chronic*

1. Latent (asymptomatic)
2. Nephrotic
3. Hypertensive
4. Active and Recurrent Active
5. Malignant Hypertension

#### ACUTE DIFFUSE GLOMERULONEPHRITIS

The disease may occur in one of two forms, (1) silent (asymptomatic or insidious) and (2) overt (symptomatic). Hemolytic streptococcal respiratory infections precede the on-

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iciency with or without hypertension and edema may be seen in very severe cases.

**DIAGNOSIS.**—The diagnosis is self-evident when abnormal urinary findings, accompanied by edema and hypertension appear several days or more after the subsidence of a hemolytic streptococcal respiratory infection. It is important, however, to differentiate an initial attack of glomerulonephritis from an *exacerbation of the chronic disease* since the prognosis in the former is better than in the latter. This may be difficult, as hypertension may be found in both conditions. However, cardiac enlargement and retinal vascular disease occur in chronic glomerulonephritis if hypertension is of long duration. Acute exacerbations may develop in the nonhypertensive type of chronic disease and, unless a definite history of a pre-existent disease is elicited, it may be impossible to differentiate the initial episode from the exacerbation. Transitory hematuria and albuminuria developing *during* an acute infection are usually not due to diffuse glomerulonephritis. Hematuria and albuminuria may appear after the administration of sulfathiazole or sulfapyridine in the treatment of respiratory infections, tonsillitis and the like. It may be difficult to differentiate the toxic manifestations of these drugs from acute glomerulonephritis.

**PROGNOSIS.**—The outlook in general is good. The large majority of children recover completely. The older the patient at the onset of the initial attack, the greater is the likelihood of chronicity of the disease.

**Favorable Signs.**—Improvement which begins after a few days or in one to three weeks is favorable since, within four to six months, recovery or the latent stage will usually ensue. The indications of recovery are: increase in the volume of urine, disappearance of edema, fall in blood pressure, diminution and later disappearance of hematuria and albuminuria. The intensity of the early symptoms (albuminuria, hematuria, edema or hypertension) is no guide in prognosis. The *latent stage* is reached when edema is no longer present, the blood pressure and kidney function are normal, hematuria has practically disappeared, and albuminuria persists. Persistent albuminuria may be the only evidence of the development of the chronic form of the disease. Even after development of the latent stage, complete recovery may occur after one year and rarely after two years following the initial attack.

**Unfavorable Signs.**—Persistence of, or increase in, the severity of symptoms is unfavorable. The oliguria may become severe, the edema more extensive and nephrotic in type, vomiting and convulsions frequent, the hypertension marked, and renal insufficiency or pulmonary edema manifest. There may be

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#### TREATMENT OF "OVERT" TYPE OF ACUTE DIFFUSE GLOMERULONEPHRITIS

**Rest in Bed.**—This should be absolute until all the symptoms have disappeared and the urine has become free of albumin and red blood cells, *i.e.*, recovery has taken place. It is important early in the disease to impress upon the patient and his family that the period of bed rest may extend over many months after the more manifest symptoms have cleared up. Hospitalization may be necessary for the more seriously ill patients in order to provide more constant medical supervision. If albuminuria and microscopic hematuria persist for two to three months as the sole evidence of the disease, the patient may be permitted up.

1. *Exposure to Cold.*—The patient should be kept warm, and guarded against chilling. Flannel night clothes, sufficient coverings at night, and the avoidance of drafts are essential. Warm bed baths may be given daily.

2. *Bowels.*—Constipation is to be avoided. Laxative foods such as honey, figs and prunes may yield adequate results. Small daily doses of liquid petrolatum or milk of magnesia with an occasional enema are effective. Active purgation with saline cathartics is contraindicated.

**Dietary Treatment.**—Careful measurement of the daily fluid intake and urine volume is essential. During the first few days, especially if the symptoms are marked, the diet should be restricted to *carbohydrate* and *water*. The kidneys are thereby "spared," protein breakdown is reduced, and the danger of starvation acidosis is avoided. A total of 300 to 400 cc. of lemonade or orange juice with added dextrose may be given each day. If vomiting occurs, the vomitus is to be measured and an equivalent amount of saline solution should be given parenterally. After the first few days, the intake is increased so that the patient may have 500 to 700 cc. of fruit juices with added dextrose or sucrose. If oliguria is not a problem, the fluid intake is adjusted according to the urinary output of the previous day. The caloric needs are supplied now by carbohydrates and fats (fruit juices, soda crackers, cooked vegetables, cereal gruels, salt-free butter, cream, sugar, rice, etc.).

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Unrecognized *hypochloremia* may rarely produce anuria. The serum chloride concentration should be determined, and if it is found to be low, 10 to 15 gm. of sodium chloride in 5 to 10 per cent solution may be given intravenously.

**Heart Failure.**—The heart and blood pressure should be examined carefully throughout the course of the acute illness. A sudden rise in blood pressure, excessive intake of salt and fluid, or toxic effects upon the myocardium may precipitate heart failure. Mild dyspnea is common but no special treatment is necessary since this disappears rapidly with improvement of the rest of the clinical picture. Digitalization should be started when cardiac manifestations appear, *i.e.*, dyspnea attacks, rising pulse rate, severe persistent dyspnea, cyanosis, or rales at the bases of the lungs. If pulmonary edema develops, application of tourniquets to the extremities, injection of morphine and atropine hypodermically, administration of oxygen and rapid digitalization should be instituted. If these are unsuccessful, venesection with removal of 500 cc. of blood in adults and correspondingly less in children is to be done. Salt and fluid restriction should be maintained until all evidence of heart failure has disappeared.

**Hypertensive Encephalopathy.**—Sudden elevation of the blood pressure may precipitate headache, vomiting, amaurosis, coma and convulsive seizures. This syndrome may develop over a period of several hours and is not necessarily related to kidney function. It is therefore important to measure the blood pressure several times a day in those patients who show elevation of the blood pressure as a feature of the acute glomerulonephritis. Since hypertensive encephalopathy is the result of cerebral vascular disturbance, treatment includes measures to improve the intracranial circulation.

During the stage of *headache* and *vomiting*, magnesium sulfate, 30 to 60 cc. of a 50 per cent solution, should be given every four hours by mouth or rectum. Paraldehyde, 12 to 24

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pairment of kidney function may be absent. Many of these patients give no history of an overt attack of acute glomerulonephritis. The edema may fluctuate and finally disappear. After months or years, during which albuminuria persists, hypertension and impairment of renal function may develop.

3. *Hypertensive*.—Hypertension and slight albuminuria are the presenting features and may date from an overt acute attack. In many patients, however, there is no history of such an acute episode. The clinical course may be identical with that of "essential" hypertension, or asymptomatic chronic pyelonephritis, the patient experiencing no symptoms for years. After a variable number of years, impairment of renal function may develop. Cardiac failure or cerebral hemorrhage may be a terminal occurrence while kidney function remains normal.

4. *Active and Recurrent Active*.—Recurrent overt acute episodes or persistence of hematuria, edema and hypertension may represent the course of some patients. After a period of years, impairment of renal function and hypertension usually develop.

5. *Malignant Hypertension*.—After the patient has presented the "latent" or "hypertensive" type of chronic glomerulonephritis for a number of years, the syndrome of malignant hypertension may supervene. The onset of malignant hypertension is associated with severe headache, visual disturbances, anorexia, vomiting, weight loss and weakness. There may be impairment of cardiac or renal function. Examination in these cases reveals severe persistent hypertension, and the eyegrounds show papilledema and "cotton-wool" spots. The clinical course is rapidly progressive, terminating usually in uremia or heart failure or both.

**Diagnosis.**—Patients who have been followed since the initial attack of acute glomerulonephritis and those who give a history of an acute episode with edema, hematuria and hypertension offer no diagnostic problems.

The finding of albuminuria during a routine examination in the absence of hematuria, edema and hypertension raises the question whether the albuminuria is a manifestation of "*latent*" chronic glomerulonephritis, *benign albuminuria*, or *asymptomatic chronic pyelonephritis*. The absence of albumin in the urine voided after the patient has spent six to eight hours in the reclining position may be associated with benign albumin-

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## TREATMENT OF CHRONIC GLOMERULONEPHRITIS

It is important to remember that chronic glomerulonephritis may continue for many years without any diminution of the patient's capacity for work, etc. The most important single phase in treatment is the maintenance of adequate nutrition throughout the course of the disease. Acute exacerbations, nephrotic edema, impairment of renal function, hypertensive encephalopathy and uremia present special therapeutic problems.

**Diet.**—Undernutrition, malnutrition, or vitamin deficiencies are to be avoided in the management of patients with chronic glomerulonephritis. These patients require a diet that provides 1 gm. of protein per kilogram of body weight and in addition a surplus to replace the protein lost in the urine as albumin. Such a diet will include meat, fish, milk, and eggs as the main sources of protein. The total caloric value will depend upon the patient's weight and will be regulated by the amount of carbohydrate and fat in the diet. The diet should be supplemented by the daily administration of potent preparations of all the vitamins. Such a plan will maintain patients in nitrogen equilibrium, insure adequate nutrition and increase their resistance to intercurrent infections.

**Fluid Intake.**—If impairment of renal function exists, the excretion of a large urinary volume (1500 to 2000 cc.) may prevent uremia. If impairment of renal function coexists with edema, a large urinary volume must be maintained even though there may be an increase in the edema. To maintain a urinary volume of 1500 to 2000 cc., it is necessary to give the patient 2500 to 4000 cc. of fluid by mouth. If heart failure exists together with impairment of renal function, the fluid intake should not be restricted; strict restriction of salt should however be enforced. Restriction of salt is much more important than limitation of fluids in preventing edema.

**Salt Intake.**—The intake of sodium chloride should be restricted in the presence of edema (see *Nephrotic Type of Edema*). In the presence of impairment of renal function, salt restriction is not indicated. However, excessive intake is to be avoided.

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low. Most patients lose their desire for fluids after restriction of the salt intake. If large volumes of water are given diuresis may result, with diminution or disappearance of the edema. It is usually wise to permit the patient to drink as much fluid as he wishes, and to keep a record of the intake.

**MAINTENANCE OF A NORMAL STATE OF NUTRITION.**—The protein intake should be about 100 gm. in order to prevent malnutrition and replace protein lost in the urine. The plasma proteins may rise if the previous diet was low in protein. However, if the patient is well nourished and consumes a high protein diet, increase in the plasma proteins seldom results.

Usual amounts of carbohydrate and fat should be given to make up the caloric needs of the patient. The diet should be supplemented by the daily administration of potent preparations of all the vitamins.

**USE OF DIURETICS.**—The weight curve is a reliable index of the disappearance of edema. Despite the restriction of salt, a patient with nephrotic edema may gain weight because of the storage of calories or the increase of *nephritic edema* associated with increased capillary permeability. Diuretic drugs may be used to increase the urine volume, reduce the amount of edema, and produce a loss of weight. Before such drugs are employed, it is essential that renal function be intact and that the urine be free of or contain very few red blood cells in the centrifuged sediment.

1. *Organic Mercurial Compounds.*—These preparations may induce diuresis by diminishing the ability of the renal tubules to reabsorb water. *Mercupurin* may be given intravenously beginning with a dose of 0.5 cc. in 5 or 10 cc. of physiological saline and repeated as often as is indicated. It is wise to give as little of the drug as will yield a maximum diuretic response. Intramuscular injections of mercupurin should be avoided if marked edema of the subcutaneous tissues is present. At times the use of rectal suppositories of mercupurin may be followed by profound diuresis. A small enema should precede the instillation of the suppository. Distressing rectal symptoms may be eliminated by coating the suppository with nupercaine ointment. The drug should be given early in the morning so that the patient's sleep will not be interrupted by frequent urination.

2. *Acid-Forming Salts.*—Acid-forming salts induce mild

low. Most patients lose their desire for fluids after restriction of the salt intake. If large volumes of water are given diuresis may result, with diminution or disappearance of the edema. It is usually wise to permit the patient to drink as much fluid as he wishes, and to keep a record of the intake.

**MAINTENANCE OF A NORMAL STATE OF NUTRITION.**—The protein intake should be about 100 gm. in order to prevent malnutrition and replace protein lost in the urine. The plasma proteins may rise if the previous diet was low in protein. However, if the patient is well nourished and consumes a high protein diet, increase in the plasma proteins seldom results.

Usual amounts of carbohydrate and fat should be given to make up the caloric needs of the patient. The diet should be supplemented by the daily administration of potent preparations of all the vitamins.

**USE OF DIURETICS.**—The weight curve is a reliable index of the disappearance of edema. Despite the restriction of salt, a patient with nephrotic edema may gain weight because of the storage of calories or the increase of *nephritic edema* associated with increased capillary permeability. Diuretic drugs may be used to increase the urine volume, reduce the amount of edema, and produce a loss of weight. Before such drugs are employed, it is essential that renal function be intact and that the urine be free of or contain very few red blood cells in the centrifuged sediment.

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2. *Acid-Forming Salts.*—Acid-forming salts induce mild

1. *Acacia*.—A 30 per cent solution of acacia in 4.5 per cent sodium chloride solution is diluted with four parts of distilled water so that the resulting fluid contains 6 per cent acacia in 0.9 per cent solution of sodium chloride. A test dose of 5 to 10 gm. should first be given intravenously. Subsequent daily doses of 20 to 30 gm. are administered until 120 to 180 gm. are given. The intravenous injection of mercupurin may be successful in initiating a diuresis after a course of acacia injections has been given.

Some patients may develop an urticarial reaction, a shock-like syndrome, enlargement and tenderness of the liver or even acute uremia. Acacia tends to accumulate in the liver and remains in the serum of patients for long periods especially after repeated injections. The ultimate effects of acacia are not understood.

2. *Concentrated Solutions of Human Serum Proteins*.—The injection of concentrated solutions of human serum proteins has recently been recommended in the treatment of nephrotic edema. Until additional experience with this method of treatment is reported it would seem wise to rely upon more thoroughly tried procedures.

**Uremia**.—Uremia represents the terminal phase and is the most frequent cause of death in chronic glomerulonephritis. It is the result of renal insufficiency regardless of the pathologic process in the kidneys. While occasional cases of glomerulonephritis pursue a course without hypertension, in most cases of uremia, however, hypertension and its sequelae (heart failure, cerebral vascular episodes, neuroretinitis) are present.

The onset of uremia is usually insidious. The patient, no longer able to concentrate the urine or eliminate phenol red, shows accumulation of nonprotein nitrogenous bodies in the blood (*azotemia*). A surprisingly long period may elapse from the beginning of renal insufficiency to the onset of uremic symptoms. The initial symptoms are mental and physical fatigue, headache, loss of weight, anemia, anorexia and vomiting. As uremia progresses, nausea and vomiting become worse, with further loss of weight. Later, acidosis and coma develop. Oliguria associated with heart failure, fever, or dehydration may appear.

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(b) The daily *fluid intake* should be about 2500 cc. to insure a urinary output of at least 1500 cc. If the ingestion of such a large volume of fluid interferes with the food intake of the patient, it is wise to give it by vein as 5 to 10 per cent glucose solution or physiological saline.

2. *Acidosis*.—Acidosis is a common but not an invariable phenomenon in uremia. When it does occur, it may vary greatly in degree. It is due chiefly to retention of acid phosphates and sulfates. In a mild form, it may be overlooked. In severer degrees of acidosis, dyspnea is present. Determination of the carbon dioxide combining power of the blood will reveal low values consistent with this state.

While dyspnea due to acidosis of severe degree may be temporarily relieved by alkali therapy, it is doubtful whether such treatment actually prolongs life. Usually the acidosis recurs or death ensues from other causes. In the presence of dyspnea and a low carbon dioxide combining power of the blood, sodium bicarbonate may be given intravenously in a 5 per cent solution of distilled water or saline in amounts of 400 to 500 cc. Determinations of the blood carbon dioxide combining power should precede and follow such injections. If the patient is not vomiting, 3 to 6 gm. of the bicarbonate, citrate or acetate of sodium may be given daily after the initial intravenous injection of alkali.

3. *Anemia*.—The anemia associated with uremia is due to the depressed function of the bone marrow. The administration of iron is without effect and may induce gastric irritation with vomiting. Transfusions of 250 to 500 cc. of perfectly compatible blood may be followed by temporary improvement.

4. *Heart Failure*.—When heart failure occurs in uremia, the salt intake should be reduced and digitalis should be given cautiously by mouth or parenterally. Unless such measures increase the output of urine, severe retention of nonprotein nitrogen of the blood results with aggravation of the uremic symptoms. The fluid intake should not be less than 1500 cc. per day. Restriction of salt is essential to lessen any tendency to edema formation. Parenteral injection of digitalis is indicated if nausea and vomiting are present. Because of the impaired excretory function of the kidneys and the danger of cumulative effects, digitalis should be given with the utmost care and evidence of the optimum effect of the drug must be

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Greater recognition of the importance, in later years, of the urinary infections of *childhood* and an appreciation of the role of congenital malformations, obstructive or otherwise, in their etiology have contributed no little to management of long-standing infections of this type.

Of all the developments in the history of urinary infections, the most revolutionary has been that brought about by the introduction of *chemotherapeutic agents*, notably the *sulfonamides*. Internal urinary antisepsis has long been the mainstay of physicians in the treatment of these conditions, but an attitude which at best might be characterized as a mild defeatism has been changed in short order to one of extreme optimism. Certain conditions, among which may be mentioned infections due to *Proteus vulgaris* and pyelonephritis of pregnancy, formerly considered almost incurable, are now treated with a considerable measure of success.

So powerful is the action of the newer drugs and so far has dependence on them progressed, that one inherent hazard in their use has been greatly increased; that is, *the danger of overlooking some serious underlying surgical condition* of which the infection is a secondary manifestation. A tendency to *treat before diagnosing* has been all too common in the past and has been aggravated by the ease with which infection may be controlled by chemotherapy at present. Disservice to the patient may result from the cure of an infection which may be the only sign of damaging obstruction, stone or malignant neoplasm. Uremia from the obstructing prostate may be deadly though unaccompanied by pyuria, and cancer needs no help from infection.

#### ETIOLOGY OF URINARY INFECTIONS

The proper management of urinary infection is dependent on an understanding of the relative importance of the etiologic factors involved in a particular case. In general, these may best be considered as falling in one of three groups: (1) those concerning the invading organism, (2) those affecting resistance,

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foreign body, trauma from various causes, sometimes very minor, may be enough to tip the balance. *Overdistention of the bladder* may initiate infection. Congenitally malformed organs seem to be particularly prone to this condition.

**Obstruction.**—Of all predisposing causes of infection, that of obstruction to free drainage is far and away the most important. So frequently is an obstructive lesion found as a background for pyuria that no diagnosis is complete which has not included a search for an obstructing lesion, and no treatment is adequate which has not eliminated any possible cause of stasis. Not infrequently such a lesion is obvious; more often it can be discovered only by thorough investigation. Among the most important of such causes are *bladder neck obstruction, calculi, urethral or ureteral stricture, pregnancy* or pressure from other extrinsic masses, diverticulum or tumor of the bladder and congenital conditions of various types. Significant obstruction with small degrees of retention, as a *compensatory hyperactivity* on the part of the bladder or kidney may exist for a considerable period during which residual bladder urine may be minimal, or anatomic changes in the kidney pelvis or ureter be very minor. The effect relative to infection, however, may be the same. Similar in effect to organic obstructions is the stasis due to neurogenic dysfunctions.

#### DIAGNOSIS

The diagnosis of the presence of urinary infection is usually not difficult; the finding of *pus* or *bacteria in the urine* is the outstanding sign. Pyuria may be only the first of many data which must be secured to fulfill the requirements of a complete diagnosis. The *symptoms* naturally fall into several groups.

1. Disturbances of the bladder function: frequency, strangury, tenesmus or pain on urination.
2. Pain referred to the affected organ: loin pain, suprapubic or perineal discomfort.
3. Constitutional disturbances: chills and fever, nausea or vomiting, loss of weight, fatigability, headache.
4. Changes in the urine: pyuria, hematuria or bacteriuria.

Any combination of symptoms from one or several groups may exist, depending on the principal organ involved, the chronicity of the process, the type of the infecting organism and the nature of the predisposing factors. *Pyuria* may be

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*its first acute phase.* Special care in catheterization in the presence of obstruction, the use of tidal drainage in retention due to neurogenic disease,<sup>3</sup> and avoidance of overdistention of the bladder are important.

### TREATMENT

The object of all treatment is to cure the symptoms and to remove the cause of the infection. Certain basic therapeutic measures are applicable to all types of urinary infections. Since, as previously noted, infections are rarely confined to one organ these may be considered as to their effect on the clinical manifestations of the infection.

#### SUPPORTIVE AND LOCAL MEASURES; SURGERY

**Acute Infections.**—**BED REST; DIET; FLUIDS.**—Bed rest is essential in febrile states; bland diet and adequate fluid intake are important. *No therapeutic agent which demands restriction of fluids possesses advantages sufficient to justify its use in acute infections except in very unusual cases.* Adequate fluid intake means at least 2000 cc. each twenty-four hours. In cases accompanied by nausea and vomiting or where dehydration is present from other causes, supplementary fluid is essential. Dehydration may exist even when the patient is taking apparently adequate fluid by mouth. Our preference is for intravenous glucose 5 per cent in saline of which 1000 to 3000 cc. each twenty-four hours is usually sufficient. Acidosis which may be present will respond to the intravenous use of sodium racemic lactate—molar solution. Lesser degrees may be combatted by oral alkalis or 2 per cent sodium bicarbonate intravenously or 5 per cent by rectum. Care should be taken not to produce alkalosis from the use of the lactate and carbon dioxide values should be followed from day to day.

**HEAT; ANTISEPTICS.**—Locally, the application of heat is valuable to relieve vesical symptoms. The hot *sitz bath* is a simple but effective method of applying this agent. Hot *rectal irrigations* are most valuable in acute prostatitis and cystitis in the male. A two-way rubber catheter inserted into the rectum for sufficient distance to assure a large volume of fluid in the rectum gives good results. A semi-upright position is desirable. The temperature of the fluid should be about 110° to 115° F. and the irrigation should continue for fifteen or twenty minutes.

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## INTERNAL MEDICATIONS

Therapy should be undertaken in the hospital in those patients presenting an acute infection associated with high fever. Patients with chronic or subacute infections may be treated while ambulatory.

At the present time there are three urinary antiseptics that deserve extended comment. These three are *mandelic acid*, *sulfanilamide* and *sulfathiazole*. The dosage and action of each drug will be discussed separately and then compared as to their relative efficiency in the treatment of these infections.

**Mandelic Acid.**—This drug has been used in the treatment of infections of the urinary tract for the past six years. Its successful action is dependent on obtaining a concentration of the drug of 0.5 per cent or greater in a urine that has a pH of 5.5 or less. Mandelic acid may be administered as the ammonium, sodium or calcium salt. The *ammonium* salt, in the form of syrup, is given in doses of 8 cc. four times a day. To avoid nausea it is best to administer this drug following meals and just before retiring at night. Therapy with ammonium mandelate may not require additional acidifying salts in order to obtain the proper reaction in the urine. *Calcium mandelate*, which apparently causes less nausea, is given in doses of 3 gm. four times a day. With this preparation some acidifying agent must be administered. Several drugs may be used; ammonium chloride in doses of from 4 to 8 gm. daily is usually sufficient. While the patient is under this form of therapy, it is essential to follow the reaction of the urine closely. In order to maintain the proper reaction, fluids should be limited to six glasses daily.

It is desirable to point out the *disadvantages* of mandelic acid therapy. In some patients, in spite of large quantities of acidifying salts, it is impossible to maintain a urine of proper acidity, and in these patients poor results are obtained. Successful therapy with mandelic acid demands an intake of fluid that is small. These patients will pass only small amounts of urine and, therefore, lose the beneficial effect of passing large amounts of dilute urine. Certainly, the advisability of limiting fluid in patients with high fever, severe infections or poor renal function is open to question.

Mandelic acid produces some *toxic effects*. Cook<sup>4</sup> finds that nausea and vomiting are the two most frequent complications.

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*Studies on the Effect of Low and High Concentrations.*—Because there are relatively few reports on the amount of sulfathiazole that is necessary to administer to these patients, we have made certain studies to elucidate this matter. In a previous study<sup>13</sup> of the action of sulfathiazole in twenty-five patients with infections of the urinary tract no correlation could be made between the concentration of the drug in the urine and the clinical response. In these patients the level of free sulfathiazole obtained in the urine varied from 32 to 456 mg. per cent. A comparative study of the effect of sulfathiazole and other sulfonamide derivatives in concentrations of 10 mg. per cent was made on the organisms isolated from these patients. It was evident from these studies that low concentrations of sulfathiazole produced marked bacteriostatic and bactericidal effects. Helmholz<sup>14</sup> has recently confirmed these observations. These studies suggested, then, that high concentrations of sulfathiazole in the urine of patients with infection were not required.

It was first necessary to determine the degree of bacteriostasis produced by various concentrations of sulfathiazole against the common urinary pathogens. In this study a pooled sample of urine with a pH of 6.5 was used as the culture medium. Sterilization was obtained by passage through a Berkefeld filter. The drug was then added to the urine to make final concentrations of 5, 10, 40, 80 and 160 mg. per cent. An inoculum was then added that would produce growth in all the drug-containing cultures so that variations in the degree of killing could be noted. The urine was incubated for twenty-four hours, following which 0.5 cc. was removed and after proper dilutions pour plates were made. The agar used in these plates contained para-amino-benzoic acid. After incubation the number of colonies were counted.

TABLE 1  
BACTERICIDAL EFFECT OF VARIOUS CONCENTRATIONS OF SULFATHIAZOLE

Sulfathiazole Mg. per 100 cc.	Number of Organisms After 24 Hours' Incubation					
	<i>Escherichia coli</i>	<i>Proteus vulgaris</i>	<i>Staphylococcus aureus</i>	<i>Staphylococcus albus</i>	<i>Streptococcus faecalis</i>	<i>Flexner</i>
Control	320,000,000	50,000,000	190,000,000	1,000,000	305,600	380,000,000
5	8	7,000,000	56	120	260,400	8
10	44	100,000	192	20	159,200	20
40	12	364	84	8	24,200	44
80	24	48	144	4	956	24
160	4	160	36	24	0	80

Table 1 shows the results of these studies. In general, it can be said that concentrations of about 10 mg. per cent cause marked killing, and that increasing the concentration does not appreciably increase the bactericidal effect in the majority of experiments. There are two exceptions to this. *Proteus vulgaris* and *Streptococcus faecalis* usually show a more marked in-

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week; if all symptoms have not subsided a thorough investigation as to the causative organism and presence of obstruction should be made. When the infecting bacterium is either *Proteus vulgaris* or *Streptococcus faecalis*, it is advisable to administer somewhat larger amounts of the drug. In these infections 1 gm. three times daily is adequate.

**Toxicity.**—The manifestations of sulfathiazole toxicity are now well known. Perhaps the most characteristic is the injection of the conjunctiva. Skin rashes occur not infrequently, and may be associated with fever. Both skin rashes and fever are seen usually about the seventh to tenth day of therapy. The more serious reactions are hemolytic anemia and toxic hepatitis; fortunately these occur only rarely. As with sulfanilamide, when these toxic reactions are encountered, the drug should be discontinued and fluids forced. Careful observation will prevent the serious reactions.

**Relative Merits of Urinary Antiseptics.**—It is our opinion that sulfathiazole is the drug of choice in the treatment of these infections. Its chief advantages over mandelic acid are ease of administration, a more marked bactericidal action against all bacteria, fluids need not be limited, the reaction of the urine does not have to be regulated, and the effective bactericidal concentration in the urine is more readily obtained. A further important advantage is that sulfathiazole may be given to patients with high fever or with poor renal function. In the latter group of cases, sulfathiazole should be administered in small doses such as 0.25 gm. three times per day. We recently treated a case with marked nitrogen retention with small doses of sulfathiazole. The clinical response in this instance was adequate. When severe vomiting occurs, the sodium salt of sulfathiazole may be administered intravenously in saline. One gram three times daily is sufficient. Sulfanilamide may be given subcutaneously in somewhat larger dosages.

What are the chief advantages of sulfathiazole over sulfanilamide? The most important advantage is the marked increase in the bactericidal action of the thiazole compound. Not only does it exhibit an increased killing effect against *Escherichia coli*, *Proteus vulgaris*, *Staphylococcus aureus* and *albus*, and the *typhoid-dysentery* organisms, but it is the only agent that appears to exert any effect on *Streptococcus faecalis*. As was pointed out above, sulfathiazole is effective in low concentrations, whereas sulfanilamide, in order to exhibit bactericidal

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times difficult to detect by abdominal palpation in a freshly operated case and trauma of overdistention renders the bladder susceptible to infection. After one or two catheterizations incomplete bladder function may be established, but with residual urine, which again invites infection.<sup>16</sup> Measures which may be taken to prevent postoperative infection include the use of prostigmin, 1 cc. intramuscularly every four hours to stimulate voluntary micturition, the establishment of adequate drainage by the indwelling catheter if distention occurs, the demonstration of no residual urine after reestablishment of bladder function and the prophylactic use of sulfathiazole, 0.25 gm. t.i.d.

**Pyelonephritis of Pregnancy.**—Formerly considered rarely curable during the duration of pregnancy, this condition may be treated successfully by chemotherapy, negative cultures having been secured in numerous instances.<sup>17</sup> So far as present evidence is trustworthy, no particular danger to the fetus is involved, and doses may be used as in nonpregnant cases. In refractory cases ureter catheterization should be done, and fulminating infections may demand termination of the pregnancy.

**Infections in Childhood.**—In spite of marked progress<sup>18</sup> in the approach to this problem during the past few years, there still exists, in many quarters, a disposition to delay investigation of the urinary tract in children. Cystoscopy and other instrumentations are tolerated fully as well by children as by adults and the incidence of congenital obstructive lesions as a cause of infection is high.<sup>19</sup> The age of this group of patients, however young, is no contraindication to procedures which would be indicated under similar circumstances in an adult.

### CONCLUSIONS

Urinary infections of various types are extremely responsive to chemotherapy, the most effective agent being *sulfathiazole*.

Small doses of this drug appear to be adequate and it should be administered in a dosage of 0.5 gm. three times daily. Even smaller doses may be used when renal insufficiency exists.

Therapy should be guided by bacteriological studies.

Since most urinary infections result from some predisposing factor, a *complete diagnostic survey* should be made in chronic

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we have something as good or better. Let anyone who doubts this statement be faced with a choice between equally available formula and breast milk for the feeding of a sickly or immature infant, and see which he will choose. Moreover, because of the numerous agencies for the collection of breast milk, the tested means for its preservation and the modern facilities for rapid transportation, this food has become surprisingly available to many sections of the country.\*

If the pediatrician has breast milk available for his patient, there are practically no problems of infant feeding. If, on the other hand, he must use a substitute for it, the proper combining of milk, added carbohydrate and water should be a simple process. Unfortunately, so much mystery still clings to the matter from past days, and so much apprehension is often thrown around it by the mother's or grandmother's concern when the baby has a green stool after a bottle or in some other way behaves abnormally, that the physician is apt to lose confidence in his knowledge and turn to one of those ready-made mixtures, whose wide use must not be taken as a valid indication that they are entirely satisfactory. As a matter of fact, it is as easy to construct an adequate formula for a baby as it is to order a certain number of measures of this or that proprietary product, and it gives the doctor the great advantage of prescribing a flexible regimen, to say nothing of the advantage that it may give the parents in the way of economy.

\*Mother's Milk Directories are now located at the following addresses, which here are listed alphabetically by states. Many of these Directories are able to ship breast milk immediately by air-mail: California Babies Hospital, Los Angeles, California; Mother's Milk Bureau, Board of Health, Chicago, Illinois; Cradle Society, 2039 Ridge Avenue, Evanston, Illinois; St. Margaret's Hospital Guild, Indianapolis City Hospital, Indianapolis, Indiana; The Dispensary for Mother's Milk, Inc., 226 East Chestnut Street, Louisville, Kentucky; The Directory for Mother's Milk, Inc., 221 Longwood Avenue, Boston, Massachusetts; Woman's Hospital, 432 Hancock Avenue East, Detroit, Michigan; Clinic for Infant Feeding, Division of Community Health Service, 112 Louis Street, N.W., Grand Rapids, Michigan; The Children's Hospital, Buffalo, New York; The Children's Welfare Federation of New York City, 435 Ninth Avenue, New York City; Syracuse Memorial Hospital, 736 Irving Avenue, Syracuse, New York; Mercy Hospital, Toledo, Ohio; St. Vincent's Hospital, Toledo, Ohio; Pennsylvania Hospital, Philadelphia, Pennsylvania; Hospital for Sick Children, Toronto, Ontario; The Registry for Mother's Milk, Halket and Forbes, Pittsburgh, Pennsylvania; Royal Victoria Hospital, Montreal, Quebec; Memorial Hospital, Smith and Lamar, Houston, Texas; San Antonio Section, National Council of Jewish Women, 1023 West Poplar St., San Antonio, Texas.

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**Minerals.**—The mineral content in milk is a subject of great importance and a detailed discussion would be out of place here. Suffice it to say that, perhaps because baby calves have to grow faster than do human babies, cow's milk contains three or more times as much of the essential minerals as does human milk, except for iron which is about twice as high in human as in cow's milk. However, this is not an important difference because of the fact that there is so relatively little of this element in either. The other minerals are sufficiently high in cow's milk so that any ordinary formula supplying sufficient calories will also supply sufficient of these substances.

**Vitamins.**—The vitamin content of whole milk is apparently satisfactory as regards vitamins A and B complex in the usual formulae. Vitamins C and D are so slightly present in both pasteurized and unpasteurized cow's milk that their presence can practically be discounted.

Now with this knowledge of the substances with which we have to deal, it should be possible to establish the validity of each step in the preparation of common formulae and turn out something very like human milk. Unfortunately, while we can give a reason for each step in modifying milk, the resulting product is not human milk. As a matter of fact, Powers pointed out several years ago that the popular mixtures are as unlike human milk as they are unlike unmodified cow's milk. What has been arrived at after years of the somewhat blind process of trial and error called experience has been a lowering of the protein proportion of cow's milk, a dilution of the perhaps unnecessary amount of fat, an increase in the carbohydrate, and, by the process of boiling the milk or using evaporated milk, an ultimate product which although admittedly different in composition from breast milk is nevertheless similar to it in at least three respects: it forms a fine, soft curd on gastric digestion; it is clean and relatively sterile; and it satisfactorily nourishes the great majority of infants. An occasional infant with a severe nutritional disturbance may do well when fed milk further modified by the addition of acid substances, but such preparations have not found sufficient use in this clinic to suggest their discussion here.

#### CALCULATION OF FORMULAE

**Caloric Requirements.**—The starting point in constructing a baby's feeding program is to determine his total caloric requirement. There are two ways to do this and neither, if used alone, results in complete and universal success. The first way is to calculate how much the infant requires by multiplying his

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slightly less) of these calories should come from added carbohydrate, two thirds (or slightly more) from the milk used. If 360 calories be sought instead of 350 (and for convenience, a difference of 10 or 20 calories either way is justified), it becomes simple to specify two thirds, or 240, of these from milk (12 ounces), and one third, or 120, from sugar (1 ounce). Obviously, except for very concentrated formulae infrequently employed, the mixture ultimately arrived at should contain about as many calories per ounce (or be about "as strong") as breast milk. This allows us 1 ounce total volume for each 20 calories of food, and brings us to a total volume of 18 ounces. The formula then becomes:

Milk .....	240 calories ( $\div 20 =$ )	12 oz.
Added carbohydrate	$\left\{ \begin{array}{l} \text{Sugar} \\ \text{Syrup} \\ \text{Dextri-} \\ \text{maltose} \\ \text{Lactose} \end{array} \right\}$	.... 120 calories ( $\div 120 =$ ) 1 oz.
Water to make .....		18 oz.

This method always supplies a sufficient caloric requirement and a proper amount of fluid; the protein component will always be over  $1\frac{1}{2}$  and not so high as 2 ounces per pound. The user of this method will learn to welcome certain amounts as being easily divided into convenient thirds for fractions of carbohydrate ounces, he will find 120, 180, 270, 360 and so on up to 720 calories to be quantities which always "come out right," but if an infant requires some less handy number of calories, it can always be approximated by slightly increasing the milk component. Thus, if, as is bound to happen, our 7-pound infant gains in weight to 8 pounds with associated gain in strength and need for food, it will be easy to offer not 360 calories, but 400, as:

Milk .....	14 oz. =	280 calories
Added carbohydrate .....	1 " =	120 "
Water to make .....	20 "      400 "	

Here the milk and added carbohydrate are not exactly in proportions of two thirds to one third, but sufficiently near, and at least not in the unsatisfactory range in which more than one third of all the calories are from sugar. Obviously, when

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has its administration been that one can go into any one of the several obstetrical nurseries in the Boston area and say, "Offer this baby 3 ounces of BLI No. 3 every four hours," with complete certainty that the patient will receive the mixture described.

If this simple preparation be so justifiedly popular, why then condemn the proprietary concentrates and powders? For one reason, because they can be modified further only by dilution or concentration, not with respect to their various components; whereas a mild nutritional disturbance in an infant taking the described formula may be met by omitting a portion of the added sugar, by removing some of the fat by total or partial skimming of the milk used, or by both procedures. Just as these may have been removed suddenly, they may be restored gradually. Moreover, the carbohydrate and the water may be withdrawn by almost imperceptible gradations, when, at seven to nine months, the infant is ready to take whole unmodified milk. These things cannot be done with the proprietary products.

**Replacement of Formula by Whole Milk.**—Here we may describe how the process of replacing formula with whole milk works out. At seven months the infant weighs perhaps 15 or more pounds and we find that, aside from some energy obtained from cereal or vegetables, he needs perhaps 700 calories from the formula and is thus receiving:

Whole milk .....	24 oz. = 480 calories
Added carbohydrate ..	2 " = 240 "
	<hr/>
Water to make .....	36 " = 720 "

Any further increase in added carbohydrate as a milk modifier is not only unwise, but unnecessary, since carbohydrate has been introduced as cereal and vegetable. We may, therefore, instruct the mother each week to remove  $\frac{1}{2}$  ounce of carbohydrate and 2 ounces of water and to add 1 ounce of milk. In two weeks the mixture has changed from that stated above to:

Whole milk .....	26 oz. = 540 calories
Added carbohydrate .....	1 " = 120 "
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Water to make .....	34 " = 660 "

and in a month to:

Whole milk .....	28 oz.
Added carbohydrate ..	0 "
Water to make .....	32 "

and ultimately to plain milk.

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only when the bottle food is introduced in the first few days of the baby's existence; after that time, if the bottle is used simply as a replacement for a failing breast supply, no disturbance need be anticipated and no special deviations of proportions made. Indeed, so smoothly do infants alternate from breast milk to formulae of the general proportions described above that nurses in our premature station at the Lying-in Hospital are allowed to substitute formula for breast milk if necessary, without securing the individual approval of the staff. The number of our formula-fed premature infants thus varies in inverse proportion to the amount of pooled breast milk which happens to be available, and we see no especial difference in the appetite, digestion, or progress of *well* babies as the substitutions occur.

There is an occasional newborn infant whose mother is, for sufficient reason, unable to attempt nursing and for whom a start must be made at once on formula. Here, preparations of 20 calories per ounce with as much as one third of the calories from added carbohydrate may be beyond the powers of neonatal digestion and absorption. At this period a simple and successful mixture has been one of almost equal parts of milk and water, with slightly less carbohydrate, such as:

Whole milk .....	10 oz. = 200 calories
Carbohydrate .....	$\frac{2}{3}$ " = 80 "
<hr/>	
Water to make .....	20 " = 280 "

The infant may be offered 2 ounces of this twice on the second day of life, four times on the third day, and thereafter at four-hour intervals until, at about one week of age, the formula is replaced by the 20-calorie per ounce mixture so often referred to above.

### THE MECHANICS OF FEEDING

One repeatedly encounters situations in which unimpeachable formulae offered to infants free of infection or other abnormality do not result in satisfactory progress, but actually in loss of weight, vomiting, or "spitting up," and, what is more immediately distressing, fretting or crying, so that the entire household insists the physician do something immediately,

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matter of infant, nipples, milk and feeder is a highly profitable subject for a few words between mother and doctor. Some surprising misconceptions occur, as when a mother recently complained that, in spite of everything she did, her baby *would* keep blowing bubbles up into his formula! I have found it very useful to explain the simple physics of the matter to beginners with babies. The milk must be replaced by air, and the longer the infant sucks on the nipple without letting go to allow the air to rush in, the greater will be the vacuum holding milk in the bottle, the more suction will be required by the lips and tongue, and the more air may be sucked in around the nipple. Therefore, most babies do better with a formula when the nipple is repeatedly removed from the mouth. This not only allows equalization of forces within the bottle; but it allows the infant to pause for breath, it encourages him to work harder at the nipple but for better results, and thus to feed with less dawdling. Many babies, particularly small ones, empty a nipple by closing it between the gums at the upper, or bottle, end and then exhausting its contents, but they continue to clamp down on the empty and collapsed nipple.

If the mother is taught the essentials of this process, she can also learn to think not vaguely of colic and indigestion, but specifically of air swallowed by the infant, since all of them swallow some. One thing to teach her is simple percussion of the abdomen for tympany so that she may know what she is trying to remove, and whether it is actually present, and to what degree. Another help in avoiding the postprandial mechanical difficulties comes from placing the baby on his side or his abdomen when he is returned to his bed, and if the mother's efforts to get rid of abdominal air are not completely successful, the baby may usually be made to manage the rest of the business for himself by keeping his mattress at such an angle that his head will be an inch or so above the level of his feet.

#### FOODS OTHER THAN THE FORMULA

**Vitamins.**—The infant should start taking *vitamin C* daily, either as orange juice or as a 25-mg. tablet of the pure substance, sometime during the first month. Since we have repeatedly seen scurvy develop in infants whose parents were zealously boiling the orange juice, we warn against this un-

matter of infant, nipples, milk and feeder is a highly profitable subject for a few words between mother and doctor. Some surprising misconceptions occur, as when a mother recently complained that, in spite of everything she did, her baby *would* keep blowing bubbles up into his formula! I have found it very useful to explain the simple physics of the matter to beginners with babies. The milk must be replaced by air, and the longer the infant sucks on the nipple without letting go to allow the air to rush in, the greater will be the vacuum holding milk in the bottle, the more suction will be required by the lips and tongue, and the more air may be sucked in around the nipple. Therefore, most babies do better with a formula when the nipple is repeatedly removed from the mouth. This not only allows equalization of forces within the bottle; but it allows the infant to pause for breath, it encourages him to work harder at the nipple but for better results, and thus to feed with less dawdling. Many babies, particularly small ones, empty a nipple by closing it between the gums at the upper, or bottle, end and then exhausting its contents, but they continue to clamp down on the empty and collapsed nipple.

If the mother is taught the essentials of this process, she can also learn to think not vaguely of colic and indigestion, but specifically of air swallowed by the infant, since all of them swallow some. One thing to teach her is simple percussion of the abdomen for tympany so that she may know what she is trying to remove, and whether it is actually present, and to what degree. Another help in avoiding the postprandial mechanical difficulties comes from placing the baby on his side or his abdomen when he is returned to his bed, and if the mother's efforts to get rid of abdominal air are not completely successful, the baby may usually be made to manage the rest of the business for himself by keeping his mattress at such an angle that his head will be an inch or so above the level of his feet.

#### FOODS OTHER THAN THE FORMULA

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the baby's mouth at the 10 A.M. feeding. A week or so later, or when this technic is mastered, the same food may be added at 6 P.M. These feedings ultimately become breakfast and supper, just as the 2 P.M. feeding, to which a tablespoon of vegetable may be introduced after the cereal is well taken, becomes a mid-day dinner.

Of late there has been a competitive spirit among mothers and even among physicians as to the early introduction of solids into the diet. One sees cereals begun at three, or even two months, but one also sees a definite increase in the number of very young infants with loose foul stools, distention, poor gain, and a general picture strongly suggesting the carbohydrate and fat intolerance of celiac disease. Nothing is gained and something is risked by offering cereals or vegetables to these younger infants.

**DIET SUITABLE FOR AN AVERAGE BABY FROM TEN TO  
TWENTY-FOUR MONTHS OF AGE**

**BREAKFAST:**

8-9 A.M.      Orange juice—4 oz.  
                  Cooked cereal  
                  Egg  
                  Applesauce or banana  
                  Toast or zwieback  
                  Whole milk—up to 8 oz.

**DINNER:**

1-2 P.M.      Green vegetable (spinach, carrots, peas, wax beans, squash, beets, or vegetable soup)  
                  Baked or mashed potato, or rice, spaghetti, or macaroni  
                  Scraped beef or chicken, broiled liver or liver soup (Meat to be minced until child is able to chew well)  
                  One of the following: baked apple, stewed pears, stewed apricots, junket, custard or gelatine dessert  
                  Zwieback  
                  Whole milk

**SUPPER:**

5.30-6 P.M.      Soups, broth, or cereal  
                  Stewed fruit or any of the desserts given at the noon meal  
                  Dry toast or zwieback  
                  Whole milk

Vitamin "D" in the form of.....at.....

**GIVE WATER FREELY BETWEEN MEALS.**

**DO NOT ALLOW FOODS AT OTHER TIMES THAN  
INDICATED ABOVE.**

**DO NOT COAX CHILD TO EAT.**

*Note:* Use approved milk, boiled for three minutes, until child is one year of age.

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such therapy and it became apparent that such failures of response were associated with moderately severe hepatic insufficiency.<sup>5</sup> Thus, for the adequate intermediary metabolism between vitamin K and prothrombin, still almost wholly unknown, at least one factor required is the presence of an essentially *normal* liver.

**Sources of Vitamin K.**—There are two main sources of vitamin K for human needs, an *extrinsic* source from the diet, most abundant in chlorophyll-containing plants, and an *intrinsic* derived from the bacterial flora of the gastro-intestinal tract. Dam considers the latter source the more important for human needs. The vitamin K from both plant and bacterial sources is fat-soluble, requiring the presence of bile salts for absorption. Recently the chemical structure of both forms has been determined and both have been synthesized. Both are naphthoquinone derivatives. Of great interest and significance has been the discovery that certain synthetic analogues of natural vitamin K, particularly 2-methyl-1,4-naphthoquinone, possess even greater physiological activity than the natural material. Certain of these are water-soluble and therefore may be administered by mouth without bile salts, or parenterally.

### HYPOPROTHROMBINEMIA

Vitamin K at the present moment finds its sole therapeutic use in the treatment and prevention of hypoprothrombinemia. A suggested *classification* of the clinical conditions in which hypoprothrombinemia in man may occur is therefore presented in Table 1. It will be observed that three mechanisms exist by which prothrombin deficiency may be produced: (1) nutritional deficiency of vitamin K including dietary deficiency, failure of manufacture of vitamin K by the intestinal bacterial flora and failure of absorption of the vitamin; (2) failure of production of prothrombin by the liver; and (3) increased destruction or utilization of prothrombin.

The hypoprothrombinemia of *hemorrhagic disease of the newborn* is in all probability consequent upon the initial sterility of the gastro-intestinal tract. This hemorrhagic disorder has now been successfully treated with vitamin K and prevented by the administration of this factor.<sup>6</sup> It is of interest to note that Castle in 1938,<sup>7</sup> correlating the observation that hemor-

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A *presumptive clinical diagnosis* of hypoprothrombinemia can occasionally be made when one of the conditions listed in Table 1 is associated with the existence of a hemorrhagic tendency. However, the hemorrhagic diathesis due to hypoprothrombinemia usually does not become apparent until the prothrombin falls below 30 per cent of normal. Hypoprothrombinemia of less severity than this is frequently clinically significant. Also other causes for hemorrhagic tendency in these patients may exist, particularly *vitamin C deficiency* in the intestinal disorders and *fibrinopenia* in the liver group. Thus it cannot be emphasized too strongly that vitamin K therapy should always be controlled by the performance of tests for prothrombin concentration, particularly in the preoperative group.

#### OUTLINE OF VITAMIN K THERAPY

An outline of vitamin K therapy is presented in Table 2. The recently developed synthetic compounds possessing vitamin K activity have, because of their simplicity and cheapness of preparation, their ease of standardization and their greater water solubility, almost wholly replaced the previously used concentrates of the naturally occurring vitamin. These synthetic analogues for oral use are at present largely naphthoquinone derivatives. For parenteral use and for oral use without bile salts, two types of water-soluble preparations are being employed, esters of naphthoquinone derivatives and naphthols, both of which are apparently effective.

**Indications.**—Vitamin K therapy is indicated when there exists definite evidence of hypoprothrombinemia or when a condition exists where hypoprothrombinemia is apt to develop. An extremely important variant of the latter is in the *last week*

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**Precautions.**—Certain precautions must be taken in the preoperative preparation of surgical patients. Many of these patients exhibit a certain amount of transitory or permanent hepatic insufficiency. It is therefore imperative that a prothrombin test be done immediately preceding operation in order to make sure that the prothrombin level has responded to therapy. Surgery should not be attempted unless the prothrombin concentration is greater than 75 per cent of normal. If the patient does not respond to oral therapy, parenteral therapy should be tried. If this is unsuccessful in raising the prothrombin concentration, the transfusion of fresh blood or plasma will be the only means of raising it.

**Dosage.**—The doses of the various preparations of vitamin K are presented in Table 2. With the doses recommended excellent therapeutic results have been obtained and no toxic manifestations have been observed. The margin of safety between therapeutically effective doses and toxic amounts is with vitamin K fortunately very large.

**Effects of Vitamin K in Persons with Liver Disease.**—Very recently, the response of the prothrombin level of patients with hypoprothrombinemia to vitamin K therapy has been used as a liver function test.<sup>5</sup> Persistent failure to respond despite massive therapy is apparently indicative of moderately severe hepatic insufficiency, and when the prothrombin concentration falls in the face of adequate therapy the prognosis is usually grave.

**Summary.**—To summarize briefly, vitamin K is particularly indicated in the treatment of patients with existent or latent hypoprothrombinemia associated with an essentially normal liver and in the last week of pregnancy. With the proper use of this factor there should be a significant decrease in the incidence of hemorrhagic disorders, particularly postoperative hemorrhage, and there should be essentially no cases of hemorrhagic disease of the newborn.

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**Epidemic Disease.**—We can also face the threat of an increase in epidemic disease with more hope than in 1918, although there is much to learn. The extremely low typhoid fever morbidity in the A.E.F., compared to the terrible figure for the Spanish-American War, shows the advance in that aspect of preventive medicine from 1898 to 1918. But the World War was accompanied by a tremendous increase in typhus fever in Russia and Serbia, trench fever in Europe, and respiratory disease throughout the world. The battle is not won against respiratory infections, but what has been learned about the virus of influenza recently may stand us in good stead in the next few years. Certainly there is no aspect of medicine which is so important to the success of our national defense as the prevention of epidemic disease. Therefore, this discussion will be confined to this phase of military medicine.

**Disruption of Health Standards by War.**—Although our normal public health controls are adequate to maintain an extremely high level of health in the community, war and even our present national defense effort upsets the normal distribution of population enough to create new dangers. In England we can see the problems created by modern aerial warfare at their worst. Sewage and water systems are disrupted periodically, food stores are damaged by fire and water, great numbers of people are crowded night after night into bomb shelters with poor sanitary facilities, and large masses of the population are moved from urban to rural areas. In this country civilian government must at least be prepared to face this same prospect. Military authorities already have to face the problems created by the concentration of large bodies of men in camps in rural areas and by the stationing of troops from the Arctic to the equator.

#### CLASSIFICATION OF INFECTIONS ON THE BASIS OF THEIR ETIOLOGY AND MODE OF SPREAD

The success of preventive medicine depends upon the degree to which we understand the epidemiology, etiology and immune responses to any infectious disease. Therefore, we must review the various types of infection which might be expected to endanger our population or armed forces, and classify them according to their etiology and mode of spread. The following

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## ANIMAL-BORNE INFECTIONS

1. Birds. *Virus*. Psittacosis, equine encephalomyelitis
2. Mice. *Virus*. Lymphocytic choriomeningitis
3. Rats. *Rickettsial*. Typhus  
    *Bacterial*. Haverhill fever  
    *Spirochetal*. Weil's disease, rat-bite fever
4. Rabbits. *Bacterial*. Tularemia
5. Ground squirrels and other wild rodents. *Bacterial*. Plague, tularemia
6. Herbivorous animals. *Bacterial*. Brucellosis, tuberculosis

## WOUND INFECTIONS

- Pyogenic*. Streptococcus, staphylococcus, colon bacillus, etc.  
*Anaerobic*. Gas gangrene, tetanus

Obviously a list like this includes many diseases that would be fairly rare, but such infections as influenza and malaria may become tremendous menaces. Two methods of control of infectious disease are possible: *individual prophylaxis* and *mass measures* or *sanitation*. We shall consider what can be done along these two lines under each of the main headings.

## VIRUS RESPIRATORY INFECTIONS

The respiratory infections due to viruses can probably be controlled only by immunization of the individual, since their mode of spread by droplets is such as to preclude adequate sanitary control. Furthermore, they are most contagious before the patient is aware that he is sick. Susceptibility among the nonimmune is universal, and with colds and influenza the duration of immunity conveyed by a single attack is probably fairly short-lived, although with smallpox, chickenpox, mumps and measles the immunity is generally permanent.

The greatest hazard of our military training program is the hasty crowding together of large masses of men, many of them from rural communities where their exposure to the communicable diseases of childhood has been minimal. These nonimmune men provide an ideal soil for the propagation of epidemics. During the World War the record in the military camps in this country was as follows: 38,846 cases of measles; 102,950 cases of mumps, and 473,279 cases of influenza. A few lessons seem to have been learned from this experience, and at present new men are being introduced into the camps in small groups, quarantined for two weeks before being allowed into the main camp, and these men are being toughened up gradually. The latter is extremely important. Too often in 1918 the

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**Pneumonia.**—During the past four years, interest has been centered on a disease which has been given a number of names, among them "*virus pneumonia*", "*Type X pneumonia*" and "*atypical pneumonia*". Whether this represents a single disease entity remains to be seen. These cases are characterized by a less abrupt onset than pneumococcal pneumonia, a moderate fever with slow pulse, leukopenia, a wandering type of pneumonia with patchy consolidation moving from one part of the lung to another, a dry nonproductive cough and a rather protracted course. The disease seems to be highly contagious, and a number of deaths have occurred. It resembles psittacosis more than any known infection, but proof of its etiology is lacking to date, although a number of agents have been suggested, including the rickettsia causing Q fever.

**Common Cold.**—The cold will undoubtedly be the greatest nuisance among troop concentrations. Whether all "colds" are due to a virus is unknown. Coryza is a syndrome which may be produced by an allergic mechanism, as in hay fever, by such diseases as measles and pertussis at their onset, by numerous bacterial infections of the upper respiratory passages, particularly those due to pneumococci and hemolytic streptococci, possibly the virus of influenza in certain partially immune subjects, and by a "cold" virus or group of viruses which have been studied by Dochez and his associates, and by Long. Nobody knows whether infection with these latter viruses is always the trigger mechanism for bacterial infections such as lobar pneumonia, bronchitis, acute pharyngitis and tonsillitis. Some of Smiley's work indicates that, once there is a high carrier incidence with one of the pneumococcus types, an epidemic of the common cold will set off a whole series of attacks of otitis media, mastoiditis, sinusitis and pneumonia due to that pneumococcus. It is likely that the virulent pneumococci and streptococci possess the ability to attack and infect normal people alone, but that infection with the virus of the common cold lowers local resistance to bacterial infection and increases

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of one of the sulfonamides until the temperature had been normal for forty-eight hours. The choice of drug would depend on the bacterial invader that was most prevalent. How effective this would be remains to be seen.

The most hopeful measure for the control of measles and influenza is immunization. *Passive immunization* with placental extract or convalescent serum has been used extensively to modify or prevent measles, and might be used to stop an epidemic in a camp, if the number of those who had not had the disease were not too great. Were there an effective measles vaccine, its administration to all draftees who had not had measles would be indicated.

Passive immunization, although theoretically feasible, has never been used to prevent influenza. *Active immunization* is under investigation on a large scale. The International Health Division of the Rockefeller Foundation is now producing large quantities of vaccine made from chick embryos inoculated with influenza A virus and distemper virus, since the latter has been found to enhance the immunizing potency of the influenza virus. As yet no figures are available on the efficacy of this vaccine, so no conclusions can be drawn. The discovery of a second influenza virus, influenza B, may mean that both viruses will have to be included in the vaccine.

#### BACTERIAL RESPIRATORY INFECTIONS

Epidemics of hemolytic streptococcus, meningococcus and pneumococcus infections are associated with a marked rise in the number of carriers in the population. This is natural, since the greater the number of carriers the greater the statistical chance of the organism reaching the highly susceptible subjects who are the first victims in an epidemic. As we pointed out earlier, viruses such as those causing influenza or the common cold may play an important role in promoting this spread and also in lowering local resistance in the respiratory passages. The result is that those who previously have harbored virulent organisms without symptoms, now develop bacterial complications and further promote the spread of the bacteria by their discharges. Thus the respiratory infections of all types follow a seasonal incidence which tends to reach its peak in the winter months. Chilling and changes of temperature, the dryness of

of one of the sulfonamides until the temperature had been normal for forty-eight hours. The choice of drug would depend on the bacterial invader that was most prevalent. How effective this would be remains to be seen.

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Passive immunization, although theoretically feasible, has never been used to prevent influenza. *Active immunization* is under investigation on a large scale. The International Health Division of the Rockefeller Foundation is now producing large quantities of vaccine made from chick embryos inoculated with influenza A virus and distemper virus, since the latter has been found to enhance the immunizing potency of the influenza virus. As yet no figures are available on the efficacy of this vaccine, so no conclusions can be drawn. The discovery of a second influenza virus, influenza B, may mean that both viruses will have to be included in the vaccine.

#### BACTERIAL RESPIRATORY INFECTIONS

Epidemics of hemolytic streptococcus, meningococcus and pneumococcus infections are associated with a marked rise in the number of carriers in the population. This is natural, since the greater the number of carriers the greater the statistical chance of the organism reaching the highly susceptible subjects who are the first victims in an epidemic. As we pointed out earlier, viruses such as those causing influenza or the common cold may play an important role in promoting this spread and also in lowering local resistance in the respiratory passages. The result is that those who previously have harbored virulent organisms without symptoms, now develop bacterial complications and further promote the spread of the bacteria by their discharges. Thus the respiratory infections of all types follow a seasonal incidence which tends to reach its peak in the winter months. Chilling and changes of temperature, the dryness of

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**Diphtheria.**—Diphtheria is a disease which should not occur among our troops or civilians, but it doubtless will occur if the *gravis* form of infection gains headway. It could be readily eradicated if a pure toxoid were available for immunization. Unfortunately, although such a preparation has been produced experimentally, it is not yet available commercially. Ideally, all men new to the army should be Schick-tested and those giving positive reactions should be immunized with toxoid. However, toxoid as now produced contains considerable bacterial protein to which many adults are sensitive, so that its injection may lead to a severe local or even constitutional reaction. Toxin-antitoxin contains horse serum and is less effective as an immunizing agent, but can be used in adults. At present, the best plan would seem to be to Schick-test all men entering the services. Those with positive tests should be given a 1:100 dilution of toxoid intradermally. If this shows no reaction in forty-eight hours, they may receive toxoid; if it is positive, they should not be immunized until a purer toxoid is developed. Alum toxoid is generally more effective as an immunizing agent than plain toxoid, one injection of the former being sufficient to reverse the Schick test in over 95 per cent of people.

#### ENTERIC INFECTIONS

**Poliomyelitis.**—I have listed poliomyelitis as a possible enteric infection because recent studies have indicated that the virus can frequently be isolated from the stools in both abortive and paralytic cases, even after the disease has subsided, and because it has also been isolated from sewage in epidemic areas. This does not prove that it is spread by flies and feces, but it does make it clear that reasonable enteric precautions should be used in dealing with proved or suspected cases until more is known about its mode of transmission. For example, swimming in rivers contaminated with sewage should be absolutely forbidden when cases are known to be occurring.

**Typhoid and Paratyphoid Fevers.**—The bacterial infections of the intestines are an ever-present menace to large numbers of troops in the field. Despite the low typhoid rate in

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that. This is to be expected, since it acts within the lumen of the intestine rather than in the tissues, and later in the disease the bowel wall is invaded and ulcerated.

**Cholera.**—Cholera is largely an Asiatic disease at present, but if troops had to operate in that area, vaccination should be considered, since there is evidence that it is moderately effective.

**Toxic Food Poisoning.**—The toxic types of food poisoning result from the ingestion of food in which bacterial growth and toxin production have taken place outside the body. The *staphylococcus* is most often incriminated and flourishes particularly in fatty foods, such as cream and éclair fillings. Its toxin is relatively heat stable. *Botulism* is rare, but it is a danger if food spoilage occurs. Since the spores of *B. botulinus* are killed by commercial canning methods, it is of little importance except in home-canned foods. The only control of these diseases is by proper food handling.

**Protozoan Food-borne Infections.**—The prevention of protozoan food-borne infections, such as *trichiniasis*, consists in the proper inspection of meat and thorough cooking. The incidence of *trichiniasis* has been rather closely correlated in this country with the practice of feeding garbage to hogs. *Amebiasis* in the tropics must be prevented by eliminating from the diet all uncooked food that cannot be peeled.

#### VENEREAL INFECTIONS

The local prophylactic measures—condoms, careful washing with soap and water, silver proteinate instillation, and the application of calomel ointment—devised during the last war must be used in this field. The degree of effectiveness depends on how soon and how intelligently they are used. Sulfonamide prophylaxis of gonorrhea does not seem indicated, since it would have to be used too frequently, and sensitization to the sulfonamides might be induced.

#### CONTACT INFECTIONS

Cleanliness, fumigation of vermin-infested clothing, and care to avoid contact with patients in regions where diseases such as yaws, pinta and trachoma are endemic, are about all that can be done to prevent this type of infection.

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the virus remains in high titer for some days during which mosquitoes may transmit the infection to other birds, horses, man and possibly rodents. Ticks have also been found capable of harboring the virus, so that it is possible that it may survive the winter in these arthropods. Equine encephalomyelitis is not much of a menace to man under ordinary circumstances, and is less important to military men since gasoline engines have largely replaced horses. In the event of an epidemic, there is an effective vaccine available.

**Malaria.**—The mosquitoes which threaten the welfare of the Americas most are the members of the *Anopheles* group, since they transmit malaria. This disease is of tremendous military and economic importance throughout the southern United States, Mexico, Central America and northern South America, since we have no really good methods of control. Anopheline mosquitoes are wild breeders, and their extermination involves extensive draining and oiling of swamps. In recent years *Anopheles gambiae* has been imported into Brazil from West Africa. This vicious mosquito breeds around human habitations, has no natural enemies, and is very susceptible to infection, particularly with the plasmodium of aestivo-autumnal malaria. Thus epidemic malaria has followed this mosquito in its spread through Brazil, where the government and the Rockefeller Foundation are attempting to localize it. The actual control of malaria resolves itself into either sending susceptible troops to malarial areas for very short periods at a time, or giving prophylactic quinine, which serves to keep the infection latent.

**Plague.**—In our own rural areas we have a number of diseases which are actual or potential menaces to people whose outdoor life brings them into contact with wild animals or insects. Plague infection exists in many wild rodents of the West, in whom it is kept endemic by blood-sucking insects, particularly fleas. As long as there is no extensive contact with these animals or extensive flea infestation of troops, epidemics need not be feared, but the reservoir exists. In South America a few cases of plague continue to occur, and pneumonic cases were reported in Ecuador this year.

**Tularemia.**—Tularemia, like plague, is a rodent disease, kept alive among rabbits by blood-sucking insects, but one

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Zinsser, and are available against typhus and Rocky Mountain spotted fever. The best protection against these diseases under ordinary circumstances is to avoid ticks and vermin and to keep rats under control.

**Weil's Disease.**—Rats, like ticks, carry a number of infections communicable to man. In addition to plague and typhus, they harbor the organisms of Weil's disease and rat-bite fever. Weil's disease is a severe infection with fever, jaundice, albuminuria, and edema, caused by *Leptospira*, which may be acquired by contact with or ingestion of the excreta of infected animals, particularly in water or sewage. *Leptospira icterohemorrhagiae* is carried by rats, *L. canicola* by dogs, and both animals shed the organisms in the urine.

**Rat-bite Fever.**—This disease is of two types, *Haverhill fever* and infection with *Spirillum minus*. Haverhill fever is an acute febrile polyarthrititis with an erythematous rash due to the *Streptobacillus moniliformis*, which is a member of the group of pleuropneumonia-like organisms. *Spirillum minus* infection is characterized by a primary chancre and a secondary stage much like syphilis, with bouts of fever at five- to ten-day intervals. The prevention of all these infections depends on the control of rats, a difficult matter when buildings are being bombed so that the rats are constantly disturbed.

#### WOUND INFECTIONS

The pathogenesis of anaerobic wound infections is fairly well understood. Most native soil and all heavily manured soil is contaminated with the spores of the tetanus bacillus and gas gangrene organisms. Spores of the latter are found in the wool of most uniforms. When war wounds are received, soil and bits of wool are blown deep into the wound. If the spores lodge in a site where tissue necrosis occurs as a result of trauma, irritation from foreign bodies, or pyogenic infection, conditions will become sufficiently anaerobic to permit germination of the spores, and infection may result.

Thus, the most important measures in the control of these infections are *removal of all devitalized tissue and foreign bodies*, and the *prevention of pyogenic infection*. Pyogenic infection, as the British have recently emphasized, may result from the contamination of wounds with virulent staphylococci,

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#### SUMMARY

An attempt has been made to present some of our present knowledge of the epidemiology and etiology of those infectious diseases which might endanger our troops and civilians in the event of war.

Members of the armed forces should certainly be immunized against smallpox, typhoid and paratyphoid fevers, and tetanus. Those sent to the tropics should receive yellow fever vaccine. Influenza vaccine should be prepared so that it can be used if necessary in an attempt to check the spread of epidemic influenza among troops and civilians. Vaccines against typhus, Rocky Mountain spotted fever, cholera and perhaps plague should also be held in readiness in case our military forces are called upon to operate in areas where these infections are endemic.

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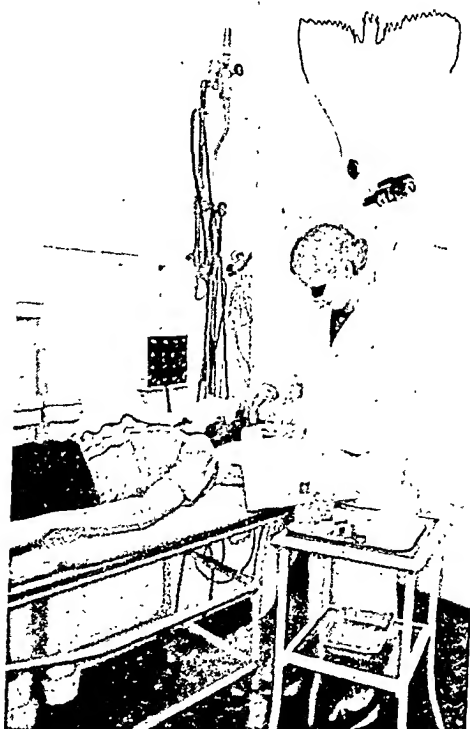


Fig. 180.—The patient lies on the litter as the electrodes are applied. Note on wall the box into which pin-jack ends of electrodes are inserted. *Inset*.—An electrode. Flat part is a simple solder disk that is fastened to the scalp. The pointed end is an ordinary pin jack for insertion into the box near the patient's head. (Figs. 180, 181, 185 appeared in the *St. Louis Post Dispatch*, Sept. 29, 1940, in an article describing the laboratory.)

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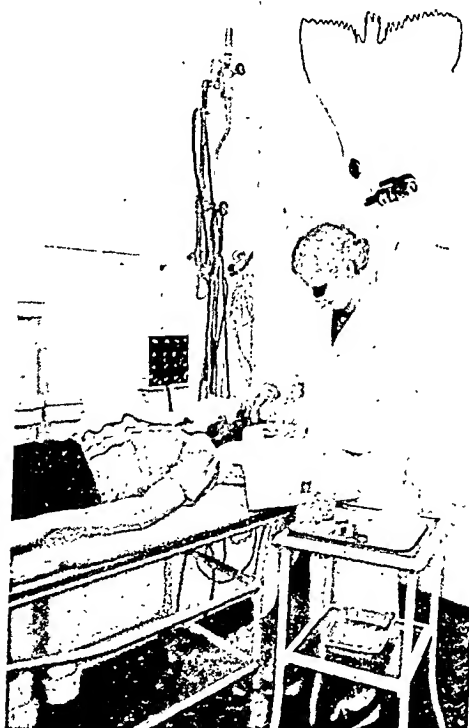


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**Artifacts.**—The clinical interpretation of these records is like that of the x-ray and the electrocardiogram. A good general training in medicine plus a knowledge of the limitation and sources of error will do more to prevent ridiculous claims of the powers of this apparatus than anything else. It is to be kept in mind that the sensitivity of the apparatus is so great that electrical disturbances in the air such as an exposed unshielded, alternating current wire or the waves from a sparking commutator of a nearby motor will introduce

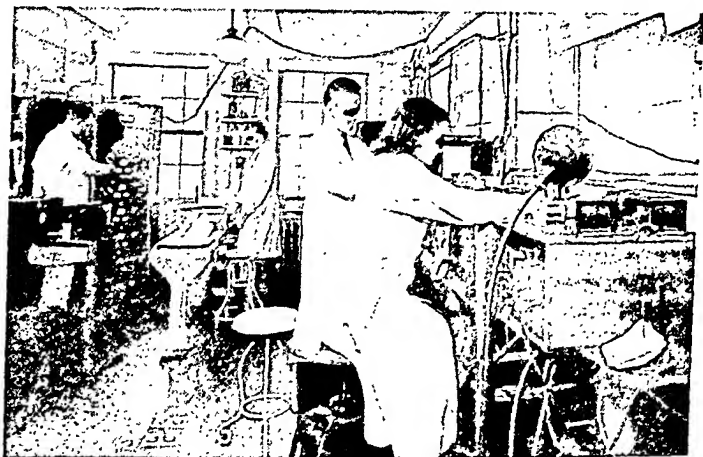


Fig. 181.—A view of the Brain Wave Laboratory showing two sets of electroencephalographic apparatus. One of these is portable, on wheels, for use in the operating room or on wards for patients too ill to be brought to the laboratory.

artifacts consisting of high-voltage, 60 per second (60 cycle) waves into the record. This type of artifact is readily identified and can usually be eliminated by suitable shielding, condensers, or grounding of the offending source of this aerial broadcast. Chewing, swallowing, frowning, tensing neck muscles, etc., introduce muscle potentials in the record that are also readily identified after a little experience, and can usually be corrected by the subject. Slow swings of the baseline with high-voltage spikes are due to gross movements of the subject that jiggle the electrodes and build up static discharges. The 2 to 3 per second, sharp-pointed waves produced by eye movements such as blinks are easily recognized after a short while, and can be stopped by having the subject fix his eyes on a point on the wall. Loose contacts, defects in the apparatus, bad batteries, short circuits and so on are identified only with experience and are not common. It is important to keep all such artifacts in mind and be thoroughly familiar with them.

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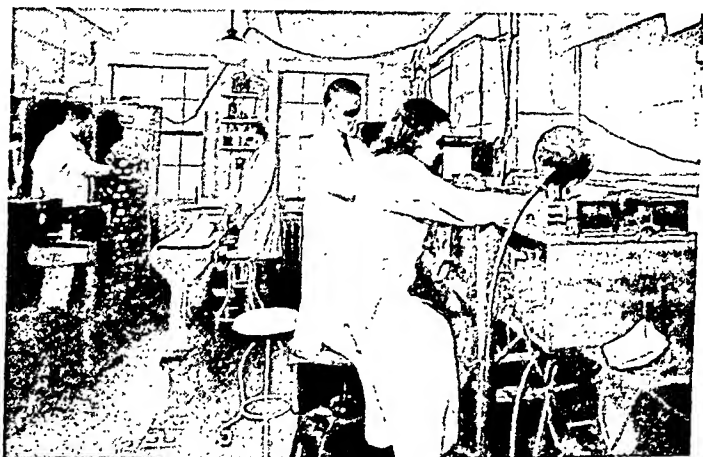


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## BRAIN WAVE PATTERNS

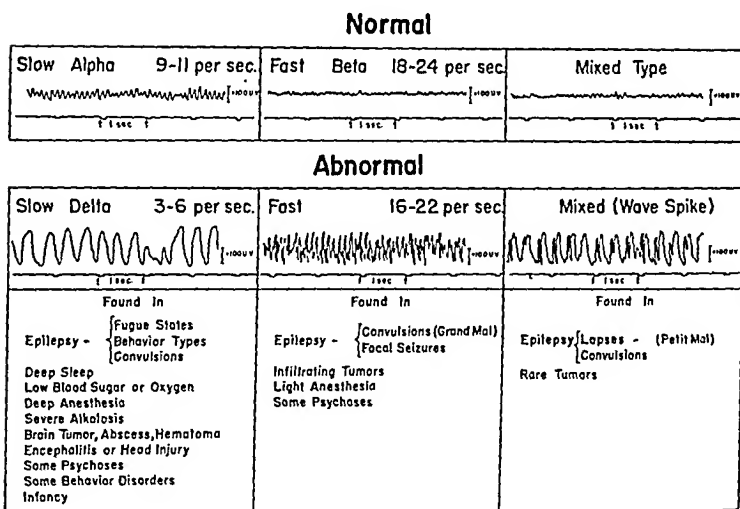


Fig. 183.—A comparison of normal and abnormal brain wave tracings arranged diagrammatically. Note higher voltage in abnormal waves and clear difference between the *normal* and *abnormal* pattern.

## ABNORMAL ELECTROENCEPHALOGRAM

There are three distinct deviations from the normal brain wave pattern encountered in the clinical laboratory:

1. The waves may become slower than 9 to 11 per second: waves from 1 to 7 per second are called *delta* or slow waves.
2. The waves may have increased voltage.
3. They may have a depressed voltage.

Pathological states of the brain are usually associated with one or more of these abnormalities. It must be pointed out here that normal electroencephalograms imply a brain *awake* and in an *adult*. Children have slower normal waves and infants may have irregular potentials as slow as 1 to 2 per second that would be grossly abnormal for an adult. Therefore, the age of the subject must be considered and corrections applied for children under twelve (Lindsley<sup>7</sup>). Furthermore, in normal sleep the waves slow down and in deep, heavy sleep around 1 A.M. (Loomis<sup>8</sup> and Kleitman<sup>9</sup>) 2 and 3 per second waves may be encountered. The subject must therefore be awake during

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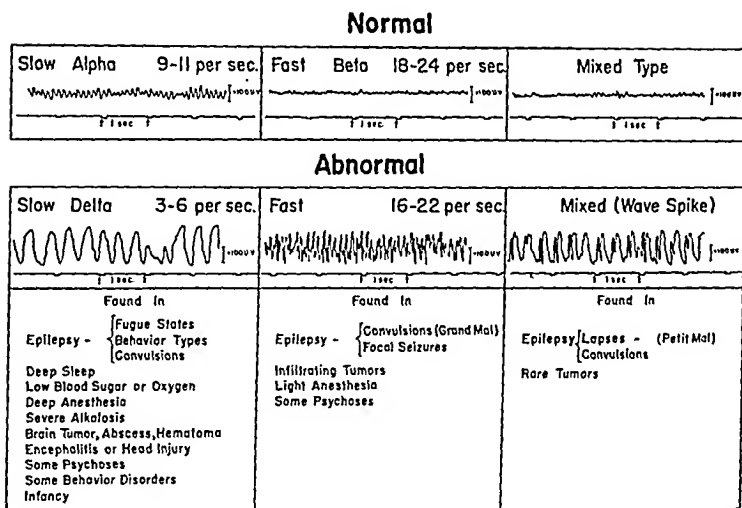


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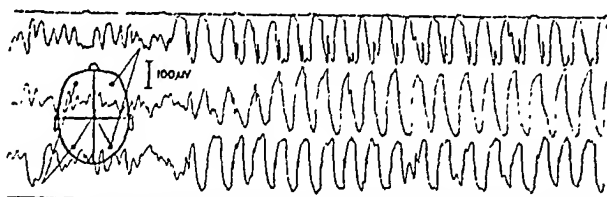
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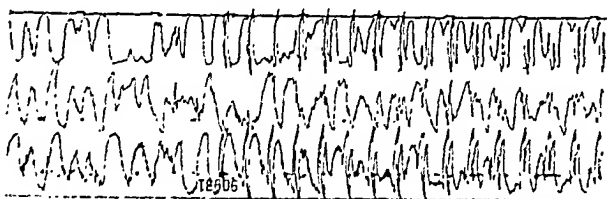
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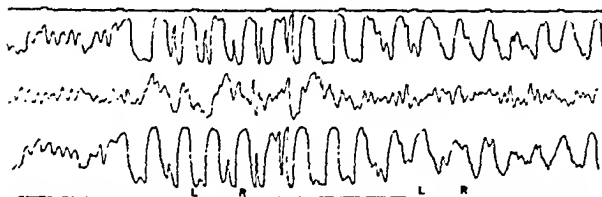
both carefully synchronized. In such a picture it is seen that wave spikes appear six to eight seconds before the movements



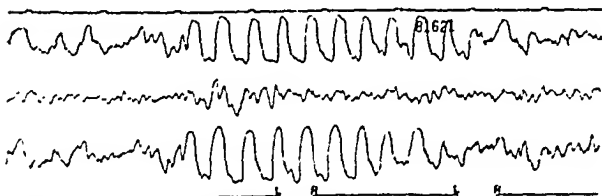
**CLINICAL DESCRIPTION OF ATTACK:** SLIGHT IMPAIRMENT OF CONSCIOUSNESS, ROLLING OF EYES, TWITCHING OF MOUTH.  
DURATION: 16 SECONDS.



**CLINICAL DESCRIPTION OF ATTACK:** SEVERE IMPAIRMENT OF CONSCIOUSNESS, ROLLING OF EYES, TWITCHING OF MOUTH AND CHEWING.  
DURATION: 20 SECONDS.



**CLINICAL DESCRIPTION OF ATTACK:** SLIGHT IMPAIRMENT OF CONSCIOUSNESS WITH STARRING OF EYES.  
DURATION: 9 SECONDS.

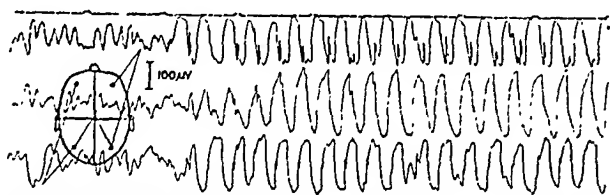


**CLINICAL DESCRIPTION OF ATTACK:** VACANT EXPRESSION OF FACE, NO MOVEMENTS.  
DURATION: 4 SECONDS.

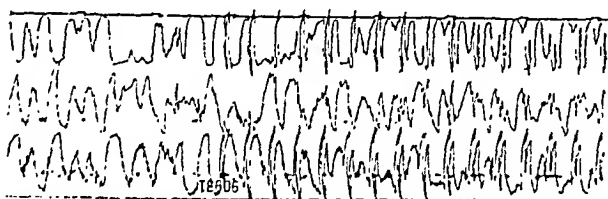
Fig. 184.—Some examples of electroencephalograms during slight attacks.

and sounds previously described are noticeable. A great many patients are unaware of the presence of these small lapses and

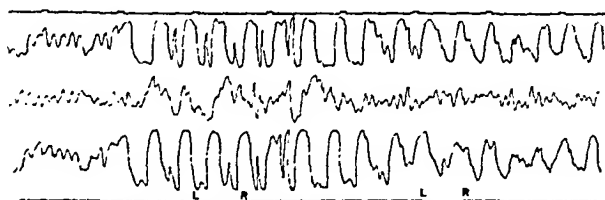
both carefully synchronized. In such a picture it is seen that wave spikes appear six to eight seconds before the movements



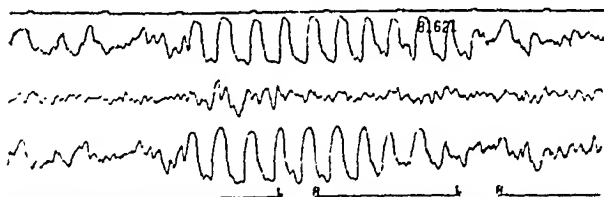
**CLINICAL DESCRIPTION OF ATTACK:** SLIGHT IMPAIRMENT OF CONSCIOUSNESS, ROLLING OF EYES, TWITCHING OF MOUTH.  
DURATION: 16 SECONDS.



**CLINICAL DESCRIPTION OF ATTACK:** SEVERE IMPAIRMENT OF CONSCIOUSNESS, ROLLING OF EYES, TWITCHING OF MOUTH AND CHEWING.  
DURATION: 20 SECONDS.



**CLINICAL DESCRIPTION OF ATTACK:** SLIGHT IMPAIRMENT OF CONSCIOUSNESS WITH STARRING OF EYES.  
DURATION: 9 SECONDS.



**CLINICAL DESCRIPTION OF ATTACK:** VACANT EXPRESSION OF FACE, NO MOVEMENTS.  
DURATION: 4 SECONDS

Fig. 184.—Some examples of electroencephalograms during slight attacks.

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## MENTAL AND NEUROLOGICAL DISORDERS

A second group of patients who show abnormal brain waves are behavior problem children; 40 per cent of all psychotics; and patients with a variety of diffuse cerebral diseases such as chorea, encephalitis and general paresis. The apparatus here simply confirms the impression that structural damage to the brain is often seen in these disorders, and gives an indication of how extensive this may be.

A fifty-six-year-old woman was admitted to the private wards because of bizarre behavior, temper outbursts, and carelessness in her personal appearance. There was a long history of psychogenic difficulties and family trouble. The findings of neurological, spinal fluid and x-ray studies were normal. Electroencephalograms showed 3 to 5 per second waves all over the head greatly increased with moderate overbreathing. Subsequent air studies showed cortical atrophy.

## BRAIN TUMORS

A third field is of interest to the neurosurgeon. Tumors, abscesses and clots usually cause a local disturbance in the brain wave pattern. By means of a multi-channel machine and the use of sixteen scalp electrodes it is possible to localize the region of this abnormal electrical activity (Williams and Gibbs,<sup>15</sup> Fig. 185).

A forty-three-year-old man was admitted to the neurological service with weakness of his left leg and attacks of numbness on his left side. Electroencephalographic examination showed a sharp focus in the upper left parietal region. Operation revealed a meningioma in this area. A month later a normal brain wave record was obtained.

In this case the neurosurgeon felt that the neurological examination, x-ray of the skull and positive electroencephalogram were enough for surgery without the need of air studies.

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Of eighty-nine doubtful or poor localizations, 44 per cent were correct. Where no electrical focus was found, the subsequent course showed a 91 per cent correct result (213 cases).<sup>10</sup> In three other laboratories similar results have been reported. It is to be emphasized here that this new method of localizing intracranial lesions must not be regarded as a substitute for other methods, such as a careful neurological examination or air studies, but as a check and *additional* tool to aid the surgeon at his task.

#### NEW FIELDS

The changes in the brain wave records are closely related to states of consciousness.<sup>13</sup> When the low oxygen—or low blood sugar—or anesthetic agents of various kinds are tried on subjects, or even animals, recording of the brain wave record proved valuable indication of whether the cerebral cortex is normal or abnormal. In the examination of aviators and automobile drivers, testing with this sort of apparatus may provide important data regarding misfits and failures.

#### SUMMARY

In 1937 the Brain Wave Laboratory of the Massachusetts General Hospital was opened. About twenty patients were examined each month. In 1941, 240 to 260 examinations are being made each month, and the test is firmly established as a part of the diagnostic procedures patients may require. It is extremely useful in aiding the diagnosis of epileptics and in following their therapy. It may differentiate abnormal behavior or psychosis of structural origin from purely psychogenic disorders. It is helpful in localizing intracranial lesions of all sorts. It is a useful tool in physiological research on the cerebral cortex, being an indicator of the level of consciousness.

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